Reasons for choosing darunavir/ritonavir 600/100 mg BID vs. 800/100 mg QD in ART-naive patients

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BACKGROUND

- Ritonavir-boosted darunavir (DRV/r) is recommended in ART-Naïve, specifically in those with perceived low adherence and before results of resistance test, due to the high genetic barrier and potency.
- DRV/r 600/100 mg twice daily (BID), is licensed for ART-experienced patients, while for ART-naïve patients the recommended dose is 800/100 mg once daily (QD).
- However, in clinical practice, a non negligible proportion of ART-naïve subjects are given DRV/r BID, with the believe of a higher potency.

AIM

The aim of this study is to identify patterns of prescription of DRV/r BID in ART-naive, by analyzing predictors of DRV/r 600/100 mg BID start vs. DRV/r 800/100 mg QD as first-line treatment

STUDY DESIGN AND METHODS

- All patients from the Icona cohort that started a DRV/r-based cART regimen from ART-Naïve in 2008-2017 were included in this analysis.
- A cross-sectional analysis was performed comparing demographics, clinical and lifestyle factors at the time of DRV/r start, comparing BID vs. QD frequency by chi-square and Wilcoxon test as appropriate.
- Univariable and multivariable logistic regression were performed to identify predictors of DRV/r BID initiation.

RESULTS

- A total of 1503 ART-naive subjects starting their first cART with DRV/r were included: 1297 subjects started DRV/r QD (86.3%) and 206 DRV/r BID (13.7%).

Patients' characteristics

- 82% male, median age (IQR) 40 years (32-48), 80% Italian
- Median HIV-RNA in DRV/r QD and BID groups were 5.1 and 5.3 log10 copies/mL (p=0.02), with 31% DRV/r BID with HIV-RNA>500,000 copies/mL (vs. 22% QD; p<0.01)
- Median CD4 counts were 260 cells/mmc for DRV/r QD and 215 cell/mmc for BID (p=0.07); 48% of DRV/r BID patients had CD4 <200/mmc (vs. 40% QD; p=0.04) **[Table1]**

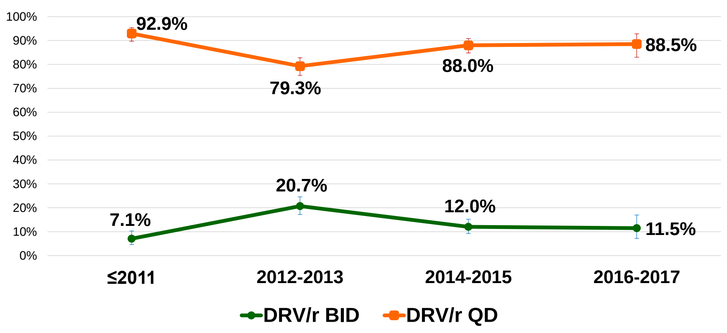
Table1 – Main characteristics of the study population at DRV/r initiation

	DRV/r QD (N= 1,297)	DRV/r BID (N=206)	p-value	Total (N=1,503)
Gender, Male, n(%)	1060 (81.7%)	173 (84.0%)	0.434	1233 (82.0%)
Mode of HIV Transmission, n(%)			0.682	
MSM	607 (46.8%)	89 (43.2%)		696 (46.3%)
IDU	79 (6.1%)	11 (5.3%)		90 (6.0%)
Heterosexual	510 (39.2%)	87 (42.2%)		597 (39.7%)
Other/Unknown	101 (7.8%)	19 (9.2%)		120 (8.0%)
Italian, n(%)	1032 (79.6%)	165 (80.1%)	0.761	1197 (79.6%)
Age, years, median(IQR)	40 (32-48)	43 (35-50)	**0.005**	40 (32-48)
Months from HIV diagnosis, median(IQR)	1.5 (0.6-12.2)	1.4 (0.5-7.9)	0.175	1.4 (0.6-11.7)
Acute HIV Infection, n(%)	31 (2.4%)	5 (2.4%)	0.974	36 (2.4%)
Site Geographical Position, n(%)			**0.001**	
North	645 (49.7%)	83 (40.3%)		728 (48.4%)
Center	507 (39.1%)	83 (40.3%)		590 (39.2%)
South	145 (11.2%)	40 (19.4%)		185 (12.3%)
CD4 count [cells/mmc], median (IQR)	260 (88-415)	215 (60-378)	0.067	256 (85-412)
CD4 count ≤200 cells/mmc, n(%)	520 (40.1%)	98 (47.6%)	**0.043**	618 (41.1%)
CD8 count [cells/mmc], median (IQR)	838 (534-1221)	745 (469-1216)	0.232	824 (523-1221)
CD4/CD8 ratio, median (IQR)	0.28 (0.14-0.46)	0.27 (0.14-0.44)	0.750	0.28 (0.14-0.46)
HIV-RNA [log10 cps/mL], median (IQR)	5.11 (4.53-5.62)	5.30 (4.58-5.79)	**0.020**	5.12 (4.53-5.65)
HIV-RNA >500.000 cps/mL, n (%)	288 (22.2%)	63 (30.6%)	**0.008**	351 (23.3%)
HCV co-infection, n (%)			0.821	
Negative	1051 (81.0%)	169 (82.0%)		1220 (81.2%)
Positive	128 (9.9%)	21 (10.2%)		149 (9.9%)
Not tested	118 (9.10%)	16 (7.8%)		134 (8.9%)
HBV co-infection, n (%)			0.193	
Negative	1072 (82.6%)	170 (82.5%)		1242 (82.6%)
Positive	50 (3.9%)	16 (6.3%)		63 (4.2%)
Not tested	175 (13.5%)	23 (11.2%)		198 (13.2%)
AIDS diagnosis, n (%)	255 (19.7%)	32 (15.5%)	0.162	287 (19.1%)
CVD diagnosis, n (%)	16 (1.2%)	1 (0.5%)	0.346	17 (1.1%)
Diabetes diagnosis, n (%)	27 (2.0%)	6 (2.9%)	0.450	33 (2.2%)
NADMs, n(%)	28 (2.1%)	2 (1.0%)	0.257	30 (2.0%)
Non-HDL Cholesterol [mg/dL], median (IQR)	114 (94-139)	115 (92-151)	0.582	114 (94-140)
HDL [mg/dL], median (IQR)	37 (29-46)	34 (27-42)	**0.018**	37 (29-45)
Glucose [mg/dL], median (IQR)	85 (79-94)	85 (80-95)	0.669	85 (79-94)

ARV regimens

- 80.4% (n=1,209) started DRV/r in a triple therapy, 5.6% (n=84) in dual regimen (81% with RAL) and 14.0% (n=210) in combination with >3 antiretroviral drugs (69% with RAL and 13% with MRV), with a higher proportion of patients on >3 drugs in the DRV/r BID group (22.3% vs 12.6%, p=0.002). 80.0% starting with TDF/FTC as NRTI backbone, 10.8% with ABC/3TC and 1.1% with AZT/3TC
- There was a peak in the use of DRV/r BID in 2012-2013 (p<0.001) **[Figure]**

Figure – Proportion of DRV/r use by frequency (QD vs. BID) according to calendar period



Predictors of DRV/r BID start

- Fitting a logistic regression model, after controlling for potential confounders **[Table2]**, older patients (>40 years: AOR=1.44; p=0.019), subjects with CD4<200 cells/mmc (AOR= 1.48; p=0.019), patients given >3 ARV-drugs (AOR= 2.11; p=0.001), patients cared by centers from southern Italy (AOR=2.57; p<0.001), patients starting first cART in 2012-2013 (AOR=2.46; p=0.001) showed a significantly higher probability of starting DRV/r BID.
- A decreased probability of DRV/r BID start was observed in AIDS presenters (AOR= 0.63; p=0.037)
- There was evidence that the use of regimens with >3 ARV was greater in people with HIV RNA >500.000 copies/mL than in those with HIV RNA ≤ 500.000 copies/mL (OR=5.9; p<0.001)

Table2 – Crude odds ratio (OR) and adjusted odds ratio (AOR) of starting DRV/r BID

	OR	95%CI	p	AOR	95%CI	p
Gender						
Female vs Male	0.85	0.78-1.74	0.434	0.79	0.52-1.20	0.281
Mode of HIV Transmission						
Heterosexual	1.00					
IDU	0.82	0.42-1.60	0.553			
MSM	0.86	0.62-1.18	0.351			
Other/Unknown	1.10	0.64-1.89	0.723			
Nationality						
Italian	1.06	0.73-1.53	0.761			
Age						
≤40 years	1.00			1.00		
>40 years	1.48	1.10-2.00	**0.008**	1.44	1.06-1.97	**0.019**
ARV Regimen Started						
≤3 Drugs	1.00			1.00		
>3 Drugs	1.98	1.38-2.86	**<.001**	2.11	1.38-3.23	**0.001**
Calendar Period of Start						
2016-2017	1.00			1.00		
2014-2015	1.05	0.62-1.79	0.849	1.24	0.72-2.13	0.438
2012-2013	2.01	1.21-3.33	**0.006**	2.46	1.46-4.13	**0.001**
≤2011	0.59	0.32-1.08	0.089	0.83	0.44-1.58	0.573
Site Geographical Position						
Northern Italy	1.00			1.00		
Central Italy	1.27	0.92-1.76	0.147	1.26	0.90-1.77	0.307
Southern Italy	2.14	1.41-3.26	**<.001**	2.57	1.64-4.01	**<.001**
Baseline CD4 count, cells/mmc						
>200	1.00			1.00		
≤200	1.35	1.00-1.82	**0.043**	1.48	1.07-2.07	**0.019**
HIV-RNA, copies/mL						
≤500,000	1.00			1.00		
>500,000	1.54	1.12-2.13	**0.009**	1.15	0.80-1.66	0.446
Hepatitis Co-Infection	0.77	0.40-1.51	0.458			
non-HDL Cholesterol per 10 mg/dL increase	1.02	0.97-1.07	0.415			
AIDS diagnosis	0.75	0.50-1.12	0.163	0.63	0.40-0.97	**0.037**

CONCLUSIONS

- Italian clinicians allocate DRV/r 600/100 mg BID as first-line regimen in several scenarios: elderly, severely immune-suppressed and highly viremic patients, frequently in regimens including more than 3 ARV-drugs and with a peak of use in 2012-2013.
- Subjects with AIDS are mostly given DRV/r QD probably due to the pill burden of concomitant medications for opportunistic infections.

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