



An observational comparison of first-line combination antiretroviral treatment (cART) with 2NRTI and ATV/r or DRV/r in HIV-infected patients in Italy

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BACKGROUND

In a recent clinical trial (ACTG 5257) no difference in virologic failure of a cART containing atazanavir/r (ATV/r) or darunavir/r (DRV/r) was found

For the endpoint of discontinuation because of intolerance, the regimen with DRV/r was superior to that of ATV/r (49% of the stops of ATV/r were attributed to jaundice or hyperbilirubinemia)

These and other intolerances to ATV/r remain a concern for clinicians who are considering to initiate treatment with a regimen including ATV/r

Overall, 330 persons discontinued ATV/r and 181 DRV/r. Figure 1 shows the distribution of reasons for discontinued stratified by third drug, as reported by clinicians. Stops due to gastro-intestinal intolerance/toxicity were similar (6% DRV/r vs. 7% ATV/r)



OBJECTIVE

To adopt the analysis plan used in ACTG 5257 to gather further information on the comparison ATV/r vs. DRV/r with longer follow-up in people seen for care in the observational setting

PATIENTS AND METHODS

Participants in the Icona Foundation Study who started cART with 2NRTI+ ATV/r or DRV/r while ART-naïve were included

Several endpoints were evaluated, similar to those defined in ACTG 5257:

- 1. A confirmed VF>200 copies/mL after 6 months of therapy
- 2. A discontinuation of DRV/r or ATV/r for any reasons
- 3. A discontinuation of DRV/r or ATV/r because of intolerance/toxicity (as reported by the treating physician)
- 4. The composite endpoint of VF or discontinuation of DRV/r or ATV/r

Statistical analysis

Survival analysis with Kaplan-Meier curves and Cox regression model stratified by clinical site was used. Participants' follow-up accrued from cART initiation to the date of the event or to the date of last available visit/viral load. The competing risk approach was used to draw the Kaplan-Meier curves of the probability of stopping due to toxicity, with administrative censoring at the last clinical visit for those stopping for other reasons

By 2 years of cART: the rate of pure virological failure was 7.6% (95% CI:5.6-9.6) in the ATV/r and 2.4% (0.9-3.9) in the DRV/r group; 9.8% (7.6-12.0) of those starting ATV/r experienced discontinuation due to intolerance/toxicity vs. 6.5% in DRV/r group (95% CI:4.2-8.8, p=0.04, Figure 2)

Figure 2. Kaplan-Meier estimates



After controlling for several confounders (footnote of Table 3) the relative hazard (RH) of discontinuation due to toxicity for ATV/r vs. DRV/r was 2.01 (95% CI:1.23, 3.28, p=0.005). Of note, this difference remained significant after controlling for current bilirubin level

RESULTS

894 persons in Icona Foundation Study who started 2NRTI+ATV/r and 686 2NRTI+DRV/r when ART-naïve on average in 2011 (IQR:2010-2012) were included. Most common NRTIs used were FTC/TDF (84%) and ABC/3TC (12%). Median age was 40 years, 22% females, 44% heterosexuals. Pts starting ATV/r were more likely to be hepatitis B/C infected (2% and 14% vs, 1% and 9%, p=0.001), they started one year earlier (2011 vs. 2012, p=0.001), were more likely to be enrolled in sites located in the north of Italy (63% vs. 54%, p=0.04), started cART less promptly after HIV diagnosis (5 vs. 2 months, p=0.02) and less likely to have started TDF/FTC (83% vs. 85%, p=0.02, Table 1). Median (IQR) follow-up was 56 weeks (21-104), with 18% (n=91) persons being followed up for longer than the trial duration of 96 weeks

Table 1. Main characteristics according to third drug started

	Third drug					
Characteristics	Darunavir/r	Atazanavir/r	p-value*	Total		
	N= 686	N= 894		N= 1580		
Gender, n(%)			0.081			
Female	134 (19.5%)	217 (24.3%)		351 (22.2%)		
Mode of HIV Transmission, n(%)			0.156			
IDU	48 (7.0%)	111 (12.5%)		159 (10.1%)		
Homosexual contacts	296 (43.3%)	314 (35.2%)		610 (38.8%)		
Heterosexual contacts	272 (39.7%)	415 (46.4%)		687 (43.5%)		
Other/Unknown	67 (9.8%)	51 (5.7%)		118 (7.5%)		
Nationality, n(%)			0.361			
Not Italian	140 (20.4%)	197 (22.0%)		337 (21.3%)		
AIDS diagnosis, n(%)			0.231			
Yes	111 (16.2%)	74 (8.3%)		185 (11.7%)		
Hepatitis co-infection [*] , n(%)			0.072			
Νο	472 (68.8%)	619 (69.2%)		1091 (69.1%)		
Yes	69 (10.1%)	139 (15.5%)		208 (13.2%)		
Not tested	145 (21.1%)	136 (15.2%)		281 (17.8%)		
Calendar year of baseline			<.001			
Median (IQR)	2012 (2011, 2013)	2011 (2010, 2012)		2011 (2010, 2012)		
Age, years			0.116			
Median (IQR)	40 (33, 48)	39 (32, 46)		40 (33, 47)		
CD4 count nadir, cells/mmc			0.089			
Median (IQR)	241 (82, 364)	275 (169, 371)		264 (131, 370)		
Viral load, log10 copies/mL			0.453			
Median (IQR)	4.93 (4.19, 5.46)	4.73 (4.02, 5.26)		4.82 (4.09, 5.35)		
Diabetes, n(%)			0.501			
Yes	6 (0.9%)	20 (2.2%)		26 (1.6%)		
Total cholesterol, mg/dL			0.895			
Median (IQR)	155 (131, 186)	161 (137, 186)		159 (134, 186)		
HDL cholesterol, mg/dL			0.338			
Median (IQR)	37 (29, 45)	39 (32, 47)		38 (31, 46)		
Time from HIV diagnosis to date of starting cART. months			0.136			
Median (IQR)	2 (1, 24)	5 (1, 39)		3 (1, 32)		
eGFR (CKD_Epi formula).				- (-,,		
ml/min/1.73m ²			0.030			
Median (IQR)	105.0 (91.64, 116.0)	105.6 (93.21, 116.5)		105.3 (92.31, 116.3)		
NRTI pair, n(%)			0.045			
Tenofovir/Emtricitabine	585 (85.3%)	738 (82.6%)		1323 (83.7%)		
Abacavir/Lamivudine	84 (12.2%)	102 (11.4%)		186 (11.8%)		
Other	17 (2.5%)	54 (6.0%)		71 (4.5%)		
*Chi-square or Kruskal-Wallis test	as appropriate					

(RH=1.78, p=0.02). There were no statistical differences detected for any of the other outcomes ($p\geq0.20$. Table 3). Contrary to the trial, the rate of viral failure tended to be higher in the ATV/r group; the big difference in the unadjusted analysis was reduced mainly by the adjustment for calendar year, NRTI-pair and mode of transmission

Table 3. Relative hazards from fitting four separate Cox regression models

	Crude and	adjusted relative hazards			
Outcomes	Crude RH (95% CI)	p- value	Adjusted [*] RH (95% CI)	p- value	
Discontinuation					
DRV/r	1.00		1.00		
ATV/r	1.18 (0.97, 1.43)	0.09	1.16 (0.92, 1.47)	0.20	
Discontinuation due to toxicity					
DRV/r	1.00		1.00		
ATV/r	1.48 (0.98, 2.22)	0.06	2.01 (1.23, 3.28)	0.005	
VF>200 copies/mL					
DRV/r	1.00		1.00		
ATV/r	3.49 (1.89, 6.43)	<.001	1.63 (0.75 <i>,</i> 3.54)	0.22	
VF>200 copies/mL or discontinuation					
DRV/r	1.00		1.00		

ATV/r

1.25 (1.02, 1.52) 0.03 1.14 (0.90, 1.45) 0.27

Adjusted for (age, gender, nation of birth, mode of HIV transmission, hepatitis co-infection status, AIDS diagnosis, nucleoside pair started, baseline CD4 count and viral load and year of starting cART

CONCLUSIONS

Our results seem to be consistent with those of the ACTG 5257, indicating a higher propensity to discontinue ATV/r for reasons due to toxicity

When viral failure, all cause discontinuations and the composite endpoint of treatment failure were considered, there was no difference between ATV/r- and DRV/r-based regimens

We cannot rule out possible bias due to unmeasured confounding or other introduced by the subjective nature of the data reported as the reason for stopping

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