Durability and tolerability of first-line combination with 2 NRTI and RAL or ATV/r or DRV/r in patients enrolled in the ICONA Foundation cohort

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Background

Although PI/r including regimens are no longer indicated as preferential regimens in the first line cART, in a number of situations they are still used as first line regimens, due to their high genetic barrier and potency.

Objectives

We aimed to conduct an analysis similar to that of the ACTG 5257 trial, comparing durability and safety of first line raltegravir (RAL) including regimens to regimens including either darunavir/ritonavir (DRV/r) or atazanavir/r (ATV/r) in the observational setting.

Methods

Participants in the Icona Foundation Cohort who started cART after the 1st of January 2008 with 2NRTI (either TDF+FTC or ABC+3TC) + ATV/r or DRV/r or RAL when ART-naïve were included.

Primary end-point: treatment failure (TF) defined by the composite endpoint of virological failure (VF) (confirmed HIV-RNA >200 copies/mL after 6 months of therapy) or discontinuation of the regimen for any cause

Secondary end-points:

- confirmed HIV-RNA>50 copies/mL after 6 months of therapy (VF50)
- discontinuation of DRV/r or ATV/r or RAL for any reasons
- discontinuation of DRV/r or ATV/r or RAL because of intolerance/toxicity (as reported by the treating physician)

Statistical analyses:

For the comparison of characteristics at time of treatment initiation among the three groups, Chi-square or Kruskal-Wallis test were used as appropriate.

Survival analysis with Kaplan-Meier curves and Cox regression model with time fixed covariates at cART initiation stratified by clinical site was used. Participants' follow-up accrued from the date of cART initiation to the date of the event or to the date of last available visit/viral load.

Results

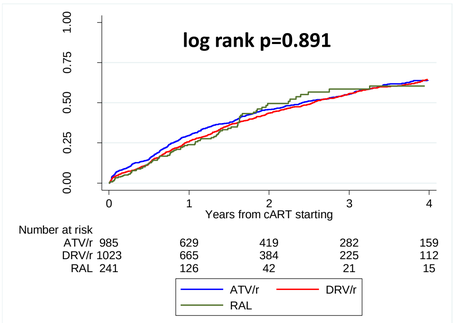
A total of 2,249 persons in Icona Foundation Cohort were enrolled: 985 started 2NRTI+ATV/r, 1023 2NRTI+DRV/r and 241 2NRTI+RAL when ART-naïve, on average in 2012 (IQR:2011-2014). Most of subjects started FTC/TDF (86.5%) as NRTI backbone. Median age was 40 years, 21% females, 44% heterosexuals. Patients starting ATV/r were less frequently males (p=0.003), less likely of Italian nationality (p=0.022), more frequently hepatitis C co-infected (p=0.001), and they started cART earlier than the other two groups (p<0.001). Subjects on DRV/r-based regimens had the lowest median CD4 cell count (p<0.001) and the highest median viral load at cART starting (p=0.001), and also the higher proportion of patients who experienced an AIDS event (p<0.001). RAL group started cART with the highest median value of CD4 count and lowest viral load (p<0.001) (Table 1).

Table 1. Main characteristics of patients according to the third drug started

CHARACTERISTICS	ATV/r N=985	DRV N=1023	RAL N=241	p	Total N=2249
Male gender, n(%)	745 (75.6%)	835 (81.6%)	196 (81.3%)	0.003	1776 (79.0%)
Age, yrs, median (IQR)	39 (32-47)	40 (33-49)	43 (35-50)	<0.001	40 (32-48)
Migrants, n(%)	240 (24.4%)	209 (20.4%)	42 (17.4%)	0.022	491 (21.8%)
Mode of HIV transmission, n(%)					
heterosexual	450 (45.7%)	426 (41.6%)	106 (44.0%)	<0.001	982 (43.7%)
PWID	118 (12.0%)	62 (6.1%)	14 (5.8%)		194 (8.6%)
MSM	354 (35.9%)	436 (42.6%)	102 (42.3%)		892 (39.7%)
other/unknown	63 (6.4%)	99 (9.7%)	19(7.9%)		181 (8.0%)
AIDS diagnosis, n(%)	88 (8.9%)	164 (16.0%)	29 (12.0%)	<0.001	281 (12.5%)
Time from HIV diagnosis to date of starting cART, months, median (IQR)	4 (1-32)	2 (1-17)	3 (1-24)	<0.001	3(1-24)
HCV co-infection, n(%)					
positive	125 (12.7%)	80 (7.8%)	19 (7.9%)	0.001	224 (10.0%)
negative	769 (78.1%)	830 (81.1%)	188 (78.0%)		1787 (79.5%)
not tested	91 (9.2%)	113 (11.1%)	34 (14.1%)		238 (10.5%)
HBV co-infection, n(%)					
positive	41 (4.2%)	37 (3.6%)	14 (5.8%)	0.311	92 (4.1%)
negative	818 (83.1%)	833 (81.4%)	190 (78.8%)		1841 (81.9%)
not tested	126 (12.8%)	153 (15.0%)	37 (15.4%)		316 (14.0%)
CD4 cell/mmc, n(%)					
0-200	267 (27.1%)	378 (37.0%)	55 (22.8%)	<0.001	700 (31.1%)
201-350	284 (28.8%)	207 (20.2%)	43 (17.8%)		534 (23.7%)
351-500	209 (21.2%)	192 (18.8%)	45 (18.7%)		446 (19.8%)
501+	133 (13.5%)	119 (11.6%)	62 (25.7%)		314 (14.0%)
not available	92 (9.3%)	127 (12.4%)	36 (14.9%)		255 (11.3%)
CD4 cell/mmc, median (IQR)	305 (171-180)	254 (91-409)	369 (180-540)	<0.001	289 (134-429)
HIV RNA cp/mL, n(%)					
50-20.000	234 (23.8%)	192 (18.8%)	66 (27.4%)	0.001	492 (21.9%)
20.000-10.000	265 (26.9%)	232 (22.7%)	60 (24.9%)		557 (24.8%)
10.000-250.000	150 (15.2%)	171 (16.7%)	30 (12.4%)		351 (15.6%)
250.000+	190 (19.3%)	240 (23.5%)	38 (15.8%)		468 (20.8%)
not available	146 (14.8%)	188 (18.4%)	47 (19.5%)		381 (16.9%)
HIV RNA $\log_{10}$ cp/mL, median (IQR)	4.8 (4.2-5.3)	5.0 (4.4-5.5)	4.7 (4.1-5.3)	<0.001	4.9 (4.3-5.4)
Calendar year of cART start, n(%)					
2008-2009	98 (9.9%)	12 (1.2%)	14 (5.8%)	<0.001	124 (5.5%)
2010-2011	354 (35.9%)	265 (28.7%)	28 (11.6%)		647 (28.8%)
2012-2013	356 (36.1%)	403 (39.4%)	52 (21.6%)		811 (36.1%)
2014-2015	177 (18.0%)	343 (33.5%)	147 (61.0%)		667 (29.7%)
NRTI pair, n(%)					
Tenofovir/Emtricitabine	852 (86.5%)	886 (86.6%)	207 (85.9%)	0.958	1945 (86.5%)
Abacavir/Lamivudine	133 (13.5%)	137 (13.4%)	34 (14.1%)		304 (13.5%)

Over a median follow-up of 2.9 years (IQR: 1.5-4.3), the 2 year-probability of treatment failure was 45.9% (95%CI: 42.7-49.2) for persons receiving ATV/r, 43.7% (95%CI: 40.4-47.0) for persons receiving DRV/r and 49.6% (95%CI: 41.3-58.4) for those receiving RAL (p=0.89)

Figure 1: Kaplan Meier estimates of reaching the different end-points stratified by third drug



KM estimates	ATV/r (N=985)	DRV/r (N=1023)	RAL (N=241)	P	Total (N=2249)
VF>50 copies/mL					
2 yrs	15.0% (12.6-17.9)	15.6% (13.1-18.5)	5.5% (2.4-12.3)	0.004	14.4% (12.8-16.4)
3 yrs	19.4% (16.4-22.8)	19.8% (16.7-23.4)	5.5% (2.4-12.3)		18.6% (16.5-20.9)
Discontinuation for any reason					
2 yrs	41.1% (37.9-44.4)	39.2% (36.0-42.6)	45.7% (37.8 -54.4)	0.784	40.4 % (38.3-42.7)
3 yrs	51.6% (48.2-55.1)	52.9% (49.3-56.6)	57.9% (48.5-67.6)		52.5% (50.1-54.9)
Discontinuation due to toxicity					
2 yrs	16.9% (14.5-19.7)	10.5% (8.5-12.8)	5.3% (2.7-10.3)	<0.001	12.9% (11.4-14.6)
3 yrs	18.4% (15.8-21.3)	13.0% (10.6-15.9)	5.3% (2.7-10.3)		14.8% (13.1-16.7)
Treatment Failure					
2 yrs	45.9% (42.7-49.2)	43.7% (40.4-47.0)	49.6% (41.3-58.4)	0.891	44.9% (42.7-17.2)
3 yrs	55.4% (52.0-58.8)	55.6% (52.0-59.3)	58.5% (49.1-68.2)		55.5% (53.1-57.9)

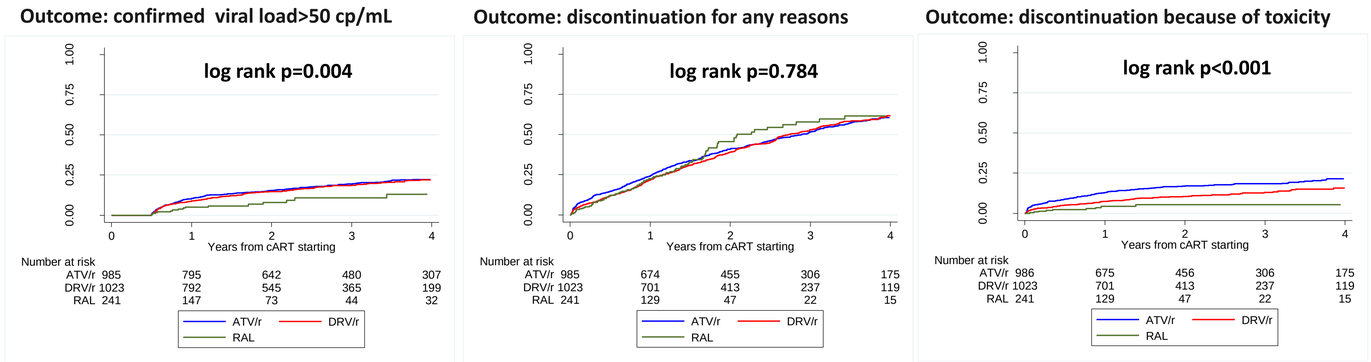


Figure 2: Distribution of reasons for discontinuation stratified by third drug

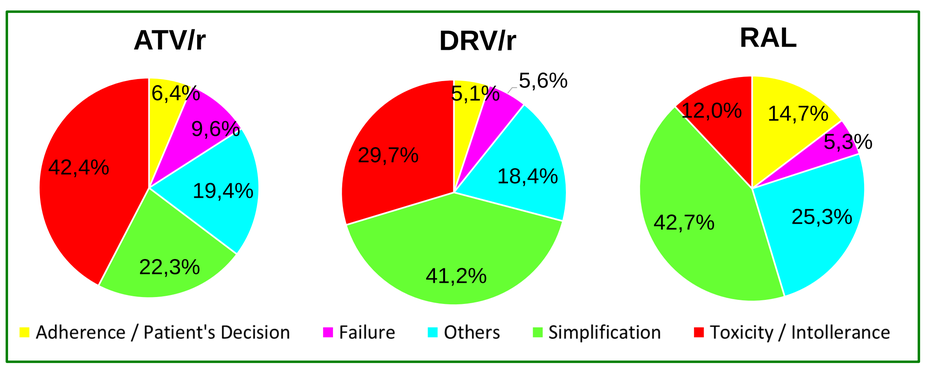


Table 2. Causes of discontinuation for toxicity

	ATV/r (N=173)	DRV/r (N=105)	RAL (N=9)
Hepatotoxicity / Hyperbilirubinemia	40,5%	5,7%	0,0%
Gastrintestinal Toxicity	14,5%	30,5%	22,2%
Allergic Reactions / Rash	13,3%	20,0%	33,3%
Others	8,1%	16,2%	22,2%
Lipidic Metabolism Toxicity	6,4%	20,0%	0,0%
Nephroxicity	13,3%	2,9%	0,0%
Toxicity Not Specified	3,5%	1,9%	11,1%
Osteopenia / Osteporosis	0,6%	2,9%	11,1%

After controlling for a number of confounders (footnote of Table 3) subjects treated with ATV/r showed a higher rate of treatment failure and of risk of discontinuation (for any reasons and due to toxicity) than the DRV/r group. In contrast, still compared to DRV/r, patients who started a RAL-based regimen showed a lower rate of discontinuation due to toxicity and a lower rate of virological failure (VF50)(Table 3).

Table 3. Relative hazards from fitting 4 separate Cox regression models

OUTCOMES	Crude RH (95%CI)	P-value	Adjusted* RH (95%CI)	P-value
TF (HIV-RNA >200 cp/mL or discontinuation)				
DRV/r	1.00		1.00	
ATV/r	1.10 (0.97-1.25)	0.138	1.19 (1.04-1.36)	0.009
RAL	0.99 (0.79-1.25)	0.950	0.91 (0.72-1.15)	0.428
VF50 (HIV-RNA>50 cp/mL)				
DRV/r	1.00		1.00	
ATV/r	0.92 (0.71-1.18)	0.496	0.99 (0.75-1.30)	0.932
RAL	0.35 (0.17-0.72)	0.004	0.42 (0.20-0.86)	0.018
Discontinuation for any reason				
DRV/r	1.00		1.00	
ATV/r	1.09 (0.95-1.24)	0.213	1.20 (1.05-1.38)	0.008
RAL	1.08 (0.86-1.35)	0.527	0.97 (0.77-1.23)	0.811
Discontinuation due to toxicity				
DRV/r	1.00		1.00	
ATV/r	1.77 (1.37-2.28)	<0.001	1.97 (1.51-2.57)	<0.001
RAL	0.47 (0.24-0.94)	0.033	0.42 (0.21-0.85)	0.017

*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 data were somewhat different from those observed in the ACTG5257 randomized comparison:
  - -when the composite endpoint of treatment failure was considered, ATV/r-based regimens showed a 19% higher risk than DRV/r
  - -when considering virological failure, with a threshold of 50 copies/mL, data are suggesting a lower rate of virological failure for RAL than DRV/r.
- ✓ In contrast, regarding the discontinuation end-point, 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 vs. DRV/r group.
- ✓ We found also a lower rate of discontinuation for toxicity in RAL-based regimens compared to DRV/r.
- ✓ ATV/r showed also a higher risk of discontinuation regardless the reason as compared to DRV/r.
- ✓ The comparison between analyses conducted in the observational settings and those coming from RCT is always a difficult one to make and we cannot rule out possible bias due to unmeasured confounding or other introduced by the subjective nature of the data reported (e.g. the reason for stopping a drug).

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