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# 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

## 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

## 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

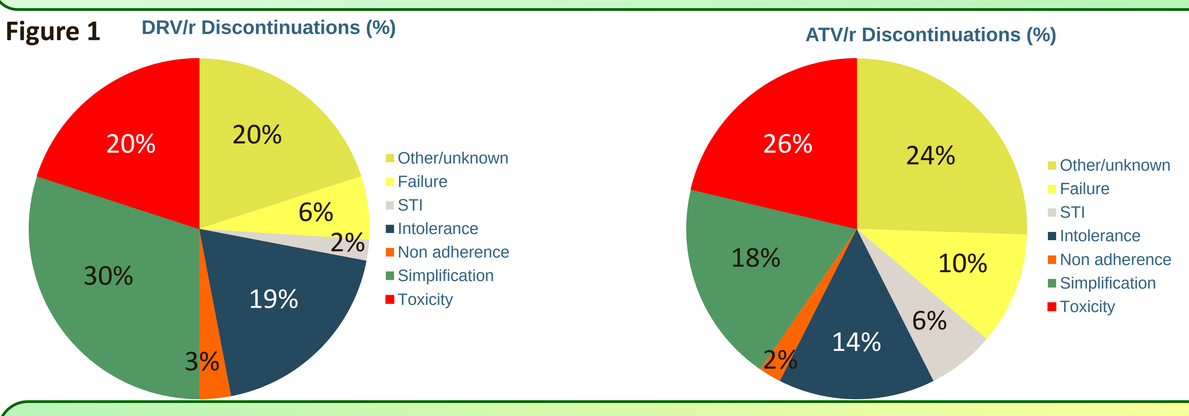
**Table 1.** Main characteristics according to third drug started

| | 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 | |
| **No** | 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/1.73m²** | | | 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

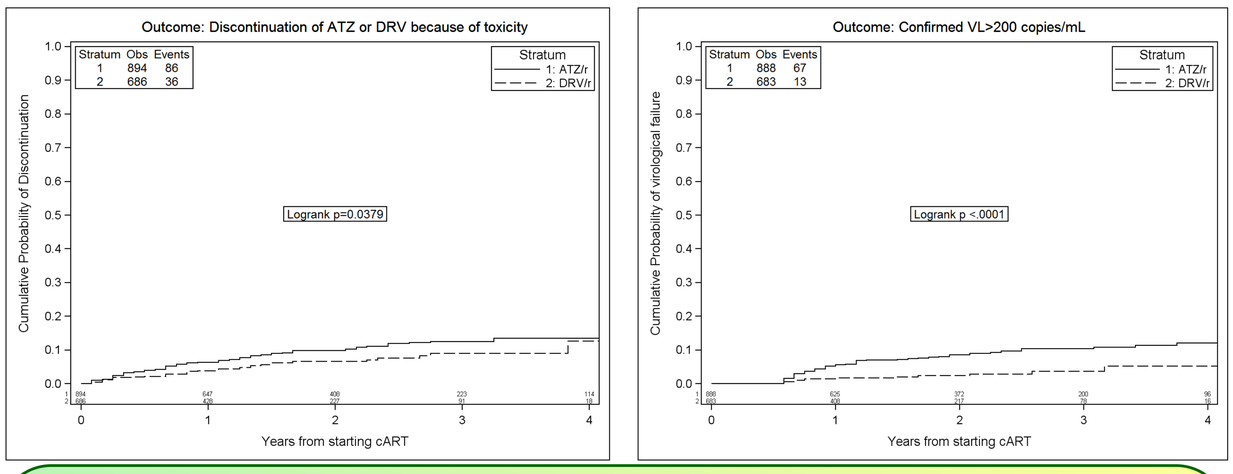
Overall, 330 persons discontinued ATV/r and 181 DRV/r. Figure 1 shows the distribution of reasons for discontinued stratified by third drug, as reported by clinicians. Stops due to gastro-intestinal intolerance/toxicity were similar (6% DRV/r vs. 7% ATV/r)

**Figure 1**




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 (RH=1.78, p=0.02). There were no statistical differences detected for any of the other outcomes (p≥0.20. 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, 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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