Reducing Number of Pills or Number of Drugs as Strategy of HIV Treatment Simplification. Data from the Italian Icona Cohort

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P101

Background

- In order to reduce toxicity and improve adherence for long term efficacy, different antiretroviral (ARV) approaches are currently available in clinical practice.
- Generally, different switching strategies are involved as reducing pill burden up one pill fixed dose combination (single table regimen – STR) or drug burden, in order to reduce regimen toxicity, up to regimens with only two or one drug (less drug regimen, LDR).

Objectives

- The present analysis aims to compare durability and effectiveness of the two approaches in patients who simplified with suppressed HIV-RNA.

Methods

- From the Italian Icona Cohort, patients who after January 2008 switched to STR or LDR from any triple drug regimen, including two NRTI plus PI/r, NNRTI or INI with undetectable HIV-RNA were selected.
  - ✓ STR included TDF/FTC plus EFV, RPV or EVG fixed dose combinations;
  - ✓ LDR included dual regimens composed by boosted PI (LPV/r, ATV/r DRV/r) plus any 3TC/FTC, MAR, RAL or ETV, and PI/r monotherapy.
- End-point of the analysis was the discontinuation of the regimen by any cause (DAC).
- Poisson regression was used to evaluate statistical associations with the outcome.

Table 1. Characteristics of patients according to type of switch to STR or LDR

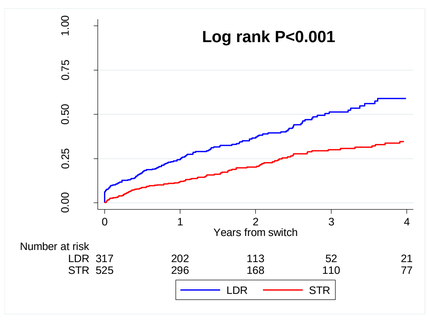
	LDR	STR	p-value
n.	317	525	
Male gender, n (%)	246 (77.6%)	418 (79.6%)	0.487
Age, years, median (IQR)	46 (39-52)	43 (36-50)	**<0.001**
Years from HIV test and first visit, median (IQR)	5.8 (2.8-15.3)	4.8 (2.4-9.8)	**0.002**
Mode of HIV transmission			
heterosexual	119 (37.5%)	201 (38.3%)	0.064
IVDU	51 (16.1%)	54 (10.3%)	
MSM	134 (42.3%)	238 (45.3%)	
Other/unknown	13 (4.1%)	32 (6.1%)	
HCV co-infection			
positive	61 (19.2%)	74 (14.1%)	0.106
negative	240 (75.7%)	429 (81.7%)	
not known	16 (5.1%)	22 (4.2%)	
HBV co-infection			
positive	10 (3.1%)	17 (3.2%)	0.970
negative	282 (89.0%)	469 (89.3%)	
not known	25 (7.9%)	39 (7.4%)	
Number of regimens at switch			
1	139 (43.8%)	315 (60.0%)	**<0.001**
2	71 (22.4%)	100 (19.1%)	
>=3	107 (33.7%)	110 (20.9%)	
Months of undetectable HIV-RNA pre-switch	25.4 (12-52)	23.2 (8-54)	0.130
Overall years of cART, median (IQR)	3 (2-8)	3 (1-6)	0.145
Laboratory data			
Haemoglobin, mg/dl	14.6 (13.5-15.5)	14.8 (13.8-15.6)	**0.026**
White blood cells	6300 (5100-7680)	5990 (5000-7300)	0.088
Triglicerides, mg/dl	133 (94-198)	121 (85-169)	**0.004**
Cholesterol, mg/dl	193 (165-221)	188 (161-217)	0.255
Creatinine, mg/dl	0.95 (0.80-1.13)	0.89 (0.78-1)	**<0.001**
MDRD, ml/min	82 (67-96)	91 (80-104)	**<0.001**
ALT, mg/dl	23 (16-33)	28 (20-40)	**<0.001**
CD4 count at switch	598 (464-807)	606 (463-805)	0.734
Type of pre-switch regimen			
NRTI/NNRTI	44 (13.9%)	197 (37.5%)	**<0.001**
NRTI/PI/r	265 (83.6%)	296 (56.4%)	
NRTI/INI	8 (2.5%)	32 (6.1%)	
Reason of switching			
Toxicity	106 (33.4%)	104 (19.8%)	**<0.001**
Adherence/patient 's decision	8 (2.5%)	15 (2.9%)	
Simplification	146 (46.0%)	278 (52.9%)	
Other/unknown	57 (18.1%)	128 (24.4%)	

Results

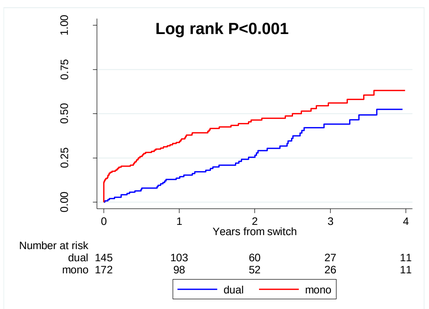
- Overall, 842 patients (525 STR, 317 LDR) were included. STR included TDF/FTC/EFV (36.8%), TDF/FTC/RPV (48.4%) and EVG/COBI/FTC/TDF (14.9%). LDR included dual regimens: LPV/r, ATV/r, DRV/r plus 3TC/FTC (29.7%), or any MVC, RAL, ETV (15.7%) and PI/r monotherapy (54.6%).
- Patients switching to STR more frequently were receiving NNRTI, were on first regimen, had higher hemoglobin, transaminase, and MDRD levels at switching as compared to LDR. In contrast, patients switching to LDR were more often on PI/r and changed for toxicity, were older, had longer history of HIV infection, had high number of previous regimens, higher triglycerides and creatinine levels (Table 1).
- Overall, 240 patients (107 STR, 133 LDR) discontinued therapy during 1525 PYFU. The crude IR of DAC was 10.8 x 100 PYFU (95%CI: 8.9-13.0) in STR and 24.9 (95%CI: 21.0-29.6) in LDR (p<0.001). Among causes of discontinuation, toxicity, as reported by the treating physician, was significantly higher in STR patients (57.0% vs. 28.6%, p<0.001).
- By multivariable Poisson regression (table 2), HCV co-infection, higher creatinine and switching from PI/r or INI were associated with higher risk of DAC; longer duration of HIV, being at second regimen vs first, and switch for simplification, as reported by treating physician were found associated with lower risk.
- Switching to STR was associated with about a 50% reduction of DAC as compared to switch to LDR. Within STR group, the risk of DAC did not differ among the three STR; while, within LDR group, probability of DAC was higher in mono than dual regimens (IRR: 1.89; 95%CI: 1.33-2.69) with no difference between 3TC/PI/r vs. other dual regimens.

Figure 1. Kaplan Meier estimates
Outcome: discontinuation for any cause

All patients, n=942



Patients who switched to LDR, n=317



Patients who switched to LDR, n=525

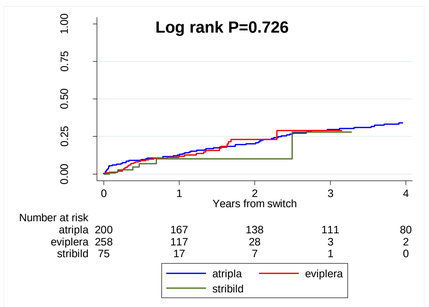


Table 2. Rate ratio of all causes discontinuation from fitting a Poisson regression.

	ARR	95% CI		p-value
Age (per 10 years older)	1.12	0.98	1.28	0.107
Years from first HIV test and visit (each)	**0.96**	**0.94**	**0.99**	**0.003**
Mode of HIV transmission				
heterosexual	1.00			
IVDU	0.85	0.50	1.44	0.548
MSM	0.76	0.56	1.02	0.063
Other/unknown	0.76	0.41	1.39	0.373
HCV co-infection				
negative	1.00			
positive	**2.01**	**1.27**	**3.17**	**0.003**
unknown	1.08	0.61	1.91	0.801
Number of regimens at switch				
1	1.00			
2	**0.60**	**0.41**	**0.86**	**0.006**
>=3	0.93	0.65	1.32	0.676
Laboratory tests				
Triglycerides (per 10 mg/dl)	1.00	0.99	1.01	0.809
Creatinine (per 10 mg/dl)	**1.31**	**1.02**	**1.67**	**0.031**
ALT (per 10 UI/l more)	1.01	0.99	1.03	0.341
Type of pre-switch regimen				
NRTI/NNRTI	1.00			
NRTI/PI/r	**1.60**	**1.14**	**2.23**	**0.006**
NRTI/INI	**2.24**	**1.19**	**4.23**	**0.013**
Reason of switching				
Toxicity	1.00			
Adherence/patient decision	1.11	0.50	2.48	0.796
Other/unknown	0.69	0.48	1.00	0.052
Simplfication	**0.65**	**0.48**	**0.89**	**0.008**
STR vs LDR	**0.54**	**0.40**	**0.73**	**0.000**

Conclusions

Reducing pill burden (STR) and reducing drug burden (LDR) are strategies that recognize different clinical reasons and settings.
Switching to STR was associated to greater stability of the regimen and consequently lower treatment discontinuation.
LDR can be useful in limited settings in order to reduce toxicity. PI/r monotherapy predicted higher rates of discontinuation.