COMPARISON OF RALTEGRAVIR AND BOOSTED DARUNAVIR VERSUS DOLUTEGRAVIR BOTH ASSOCIATED WITH TENOFOVIR/EMTRICITABINE IN PRIMARY HIV INFECTION:

VIRO-IMMUNOLOGICAL OUTCOMES OF TWO DIFFERENT INTEGRASE INHIBITOR-BASED STRATEGIES.

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BACKGROUND:

- Despite initiation of antiretroviral therapy (cART) during primary HIV infection (PHI) is now recommended by current guidelines[1,2] and its benefits have been clearly established[3], to date, the **best treatment strategy for this phase of infection is still debated**.
- **ART regimens with high genetic barrier are recommended in PHI** to allow the immediate start of therapy before genotypic resistance test (GRT) results[1,2].
- Although regimens intensified with raltegravir (RAL) have failed to demonstrate viro-immunogical advantages compared to standard ART [4-6], **the use of integrase strand transfer inhibitors (INSTIs) might add important advantages** in the setting of PHI as **rapid virological decay and early inhibition of viral integration** [7].
- The aim of this study was **to evaluate and compare viro-immunological response of a 4- versus 3-drug, both INSTI-based, regimen in the setting of PHI.**

REFERENCES:

1. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. DHHS 2017; 2 EACS guidelines version 9.0, October 2017; 3.Robb ML et al. Curr Opin HIV AIDS. 2016 4. Markowitz M et al. JAIDS 2014; 5. Chéret A et al. Lancet Inf Dis 2015: 6. Ananworanich J. JVE 2015; 7. Ambrosini J Expert Rev Antiviral Ther 2014.

METHODS:

- **Prospective, monocentric, observational study** analysing all subjects diagnosed with PHI **from July 2013 to April 2018** at INMI L. Spallanzani.
- **Diagnosis of PHI** was made if at least one of the following criteria was met: 1) positive HIV viral load (2,000 copies/mL) and negative HIV Ab/Ag Combo or Western Blot (WB) test; 2) positive HIV Ab/Ag Combo test and negative or undetermined WB test; 3) positive HIV Ab/Ag Combo test and incomplete WB test (negative p31 protein reactivity); 4) recent infection confirmed by a positive HIV-1 EIA or WB test and a documented negative HIV1 EIA within the previous 6 months.
- cART was initiated as soon as possible after HIV diagnosis, before availability of GRT, with one of the following options:
  - ✓ **4-drug group**: **RAL** 400 mg b.i.d. + **DRV/r** 800/100 mg or **DRV/c** 800/150 mg q.d. + **TDF/FTC** 245/200 mg q.d.
  - ✓ **3-drug group: DTG** 50 mg q.d. +**TDF/FTC** 245/200 mg q.d. (from May 2015)
- **Statistical analysis**
  - ✓ Follow-up accrued from the start of cART (baseline, BL) until either virological or immunological outcome achievement or last observation, for a maximum observation time of 72 weeks.
  - ✓ BL characteristics were compared between the groups using chi-square test for categorical and non-parametric tests for continuous variables.
  - ✓ **Probability of achieving virological suppression (VS:**HIVRNA <40 cp/mL**) and CD4/CD8 ratio >1** were estimated by Kaplan-Meier analysis.
  - ✓ **Predictive factors of virological suppression and CD4/CD8 ratio>1 achievement** were assesed by multivariable Cox regression model. For the virological outcome two different models were performed, excluding (model A) or including (model B) patients 'adherence to cART as a covariate.
  - ✓ **Evolution of virological and immunological parameters at each time point** was estimated by paired sample T-test.

RESULTS:

- A total of **144** patients were enrolled. Population characteristics at BL are summarized in **Table 1**.
- Over a median observation period of **18** (IQR 8-23) **months:**
  - ✓ **139/144** patients (**96.5%**) achieved **virological suppression**
  - ✓ **63/104** (**60.6%**) patients with BL CD4/CD8 ratio available and < 1 achieved **CD4/CD8 ratio>1.**
- **The 1 year-probability of achieving virological suppression was similar between the 4- and 3-drug group** [Fig1]. After stratification by pre-cART viremia**, 3-drug group showed an increased probability of achieving the virological outcome only in the stratum with BL HIVRNA <500.000 cp/mL** [Fig 2A and 2B].
- The **1-year probability of achieving CD4/CD8 ratio>1 did not significantly differ between the 4-and the 3-drug group.**[Fig 3]
- At multivariable analysis, **a more preserved immunocompetence at BL** positively predicted the **achievement of both virological suppression and CD4/CD8 ratio>1** whereas a **higher BL virological burden** was associated with a **lower probability of reaching virological control** [Table 2 and 3].
- At multivariable analysis, having started a 3-drug compared to 4-drug regimen was correlated to a better virological response [Table 2, model A]. However, **no significant association between the type of regimen and virological suppression achievement remained after controlling by patients 'adherence to cART** (suboptimal adherence defined as VAS<100) [Table 2, model B].
- **Virological decay and immunological recovery at different time points were similar between the two treatment groups** [Fig 4-6].

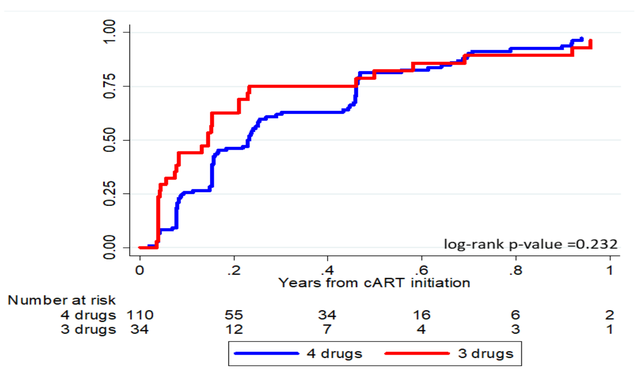
TABLE 1: BASELINE CHARACTERISTICS OF THE STUDY POPULATION

	4-DRUG REGIMEN (N=110)	3-DRUG REGIMEN (N=34)	P-VALUE
Male gender*	107 (97.3%)	31 (91.2%)	0.120
Age**	34 (26-45)	35 (28-39)	0.832
Risk Factor*			0.065
- MSM	95 (86.4%)	23 (67.7%)	
- Heterosexual	13 (11.8%)	10 (29.4%)	
- IVDU	1 (0.9%)	1 (2.9%)	
Non Italian born*	11 (10.0%)	6 (17.7%)	0.235
Days from HIV diagnosis to cART start**	5 (2-7)	6 (4-17)	**0.021**
BL CD4 cells count*			0.516
- CD4 > 500 cell/mm^3	66 (60.0%)	18 (53.0%)	
- CD4 <500 cell/mm^3	41 (37.3%)	16 (47.0%)	
Median BL CD4 cell count, cell/mm^3**	557 (379-686)	564 (383-729)	0.946
BL CD4/CD8 ratio>1*	25 (23.6%)	10 (29.4%)	0.495
BL HIV RNA *			0.524
- < 500.000 cp/ml	54 (49.1%)	14 (41.2%)	
- > 500.000 cp/ml	55 (50.0%)	19 (55.9%)	
BL HIV RNA $\log_{10}$ cp/ml**	5.7 (5.0-6.5)	5.5 (4.4-6.6)	0.503
BL HIV DNA $\log_{10}$ cp per 10^6 PBMC**	4.6 (3.8-4.9)	4.1 (3.8-4.7)	0.228
BL Fiebig stage*			0.172
- II/III	17 (15.4%)	5 (14.7%)	
- IV	35 (31.8%)	10 (29.4%)	
-V	35 (31.8%)	6 (17.7%)	
- VI	20 (18.2%)	13 (38.2%)	
Boosted PI in the regimen*			
- DRV/r	72 (65.5%)	-	-
- DRV/c	38 (34.5%)	-	-

*n (%); ** median (interquartile range)

VIROLOGICAL SUPPRESSION

FIG 1: PROBABILITY OF VIROLOGICAL SUPPRESSION (TOTAL POPULATION)

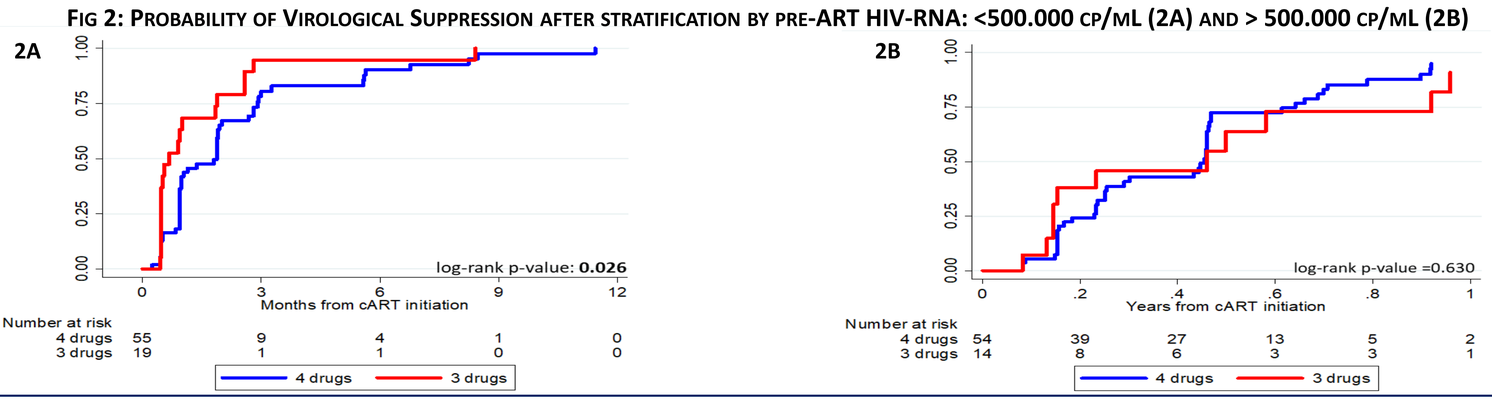


	Kaplan-Meier Estimated Probability of VS (95%CI)		
	3 months	6 months	12 months
TDF/FTC+RAL+DRV/b	**56%** (47.3-66.2)	**82%** (73.2-88.6)	**98%** (92.3-99.5)
TDF/FTC + DTG	**75%** (59.7-88.2)	**79%** (63.4-90.1)	**96%** (84.8-99.7)

TABLE 2: PREDICTIVE FACTORS OF VIROLOGICAL SUPPRESSION

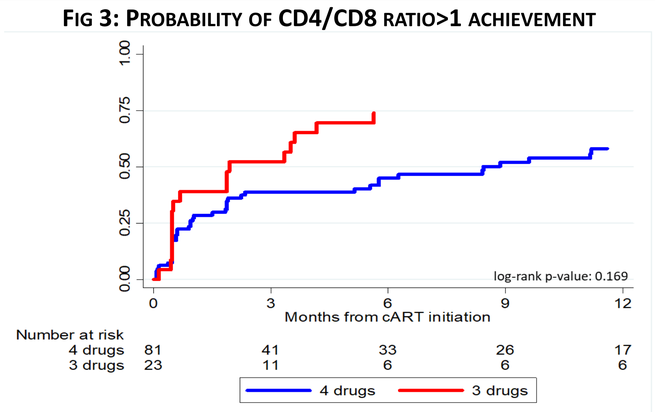
	Univariate HR (95% CI)	p	Multivariate (model A) aHR (95% CI)	p	Multivariate (model B) aHR (95% CI)	p
Female vs Male gender	2.81(1.13-6.97)	**0.026**	0.79(0.23-2.70)	0.712	1.66 (0.19-14.64)	0.648
Risk Factor						
- MSM	1	-	1	-	1	-
- Heterosexual	1.49 (0.94-2.36)	0.093	1.69 (0.90-3.16)	0.104	2.08 (1.02-4.24)	**0.045**
- IVDU	1.71 (0.23-12.45)	0.597	6.91 (0.82-58.40)	0.076	-	-
BL HIV RNA cp/mL (per 1 $\log_{10}$ higher)	0.47 (0.38-0.57)	**<0.001**	0.56 (0.44-0.72)	**<0.001**	0.68 (0.51-0.91)	**0.009**
BL HIV DNA cp x 10^6 PBMC (per 1 $\log_{10}$ higher)	0.49 (0.35-0.68)	**<0.001**	0.60 (0.40-0.90)	**0.015**	0.56 (0.34-0.93)	**0.024**
BL CD4 cell count						
- > 500 cell/mm^3	1	-	1	-	1	-
- < 500 cell/mm^3	2.08 (1.43-3.02)	**<0.001**	1.73 (1.08-2.77)	**0.021**	2.00 (1.19-3.36)	**0.009**
BL CD4/CD8 ratio >1	1.85 (1.30-2.64)	**0.001**	1.95 (1.15-3.31)	**0.014**	1.47 (0.73-2.97)	0.282
cART regimen						
• 2 NRTI +DRV/b + RAL	1	-	1	-	1	-
• 2 NRTI + DTG	1.27 (0.85-1.91)	0.244	1.75 (1.09-2.84)	**0.022**	1.30 (0.72-2,34)	0.378
Suboptimal adherence (time-dependent covariate)	0.87 (0.52-1.45)	0.597			1.34 (0.72-2.49)	0.361

FIG 2: PROBABILITY OF VIROLOGICAL SUPPRESSION AFTER STRATIFICATION BY PRE-ART HIV-RNA: <500.000 CP/ML (2A) AND > 500.000 CP/ML (2B)



CD4/CD8>1 RATIO*

FIG 3: PROBABILITY OF CD4/CD8 RATIO>1 ACHIEVEMENT



* Analysis conducted on 104 patients with baseline CD4/CD8 ratio available and <1

	Kaplan-Meier Estimated Probability of CD4/CD8>1 (95%CI)		
	3 months	6 months	12 months
TDF/FTC+DRV/b +RAL	**39%** (29.0-50.3)	**45%** (34.6-56.9)	**58%** (46.4-70.2)
TDF/FTC + DTG	**52%** (59.7-88.2)	**74%** (55.3-89.4)	**74%** (55.3-89.4)

TABLE 3: PREDICTIVE FACTORS OF CD4/CD8 RATIO>1 ACHIEVEMENT

	HR (95% CI)	p	aHR (95% CI)	p
Female vs Male gender	4.89 (1.14-20.92)	**0.032**	2.10 (0.45-9.75)	0.346
BL CD4 cell count				
- > 500 cell/mm^3	1	-	1	-
- < 500 cell/mm^3	2.25 (1.33-3.80)	**0.002**	**2.25** (1.31-3.84)	**0.003**
BL CD4/CD8 ratio (per 1 point more)	6.46 (2.22-18.78)	**0.001**	**5.89** (1.86-18.65)	**0.003**
cART regimen				
• 2 NRTI +DRV/b + RAL	1	-	1	-
• 2 NRTI + DTG	1.47 (0.84-2.56)	0.179	1.73 (0.95-3.15)	0.071

EVOLUTION OF VIRO-IMMUNOLOGICAL PARAMETERS:

FIG 4: MEAN DECAY OF HIV-RNA AT SPECIFIC TIME POINTS ACCORDING TO TREATMENT GROUP

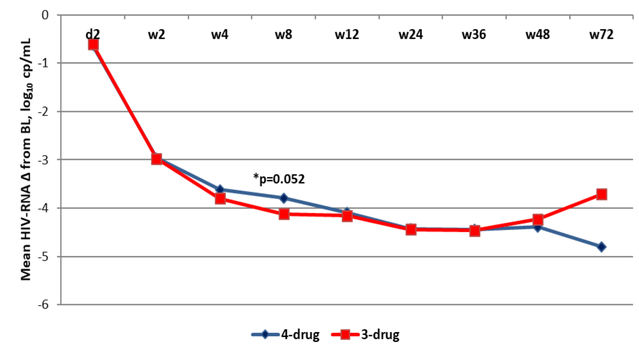


FIG 5: MEAN DECAY OF HIV-DNA AT SPECIFIC TIME POINTS ACCORDING TO TREATMENT GROUP

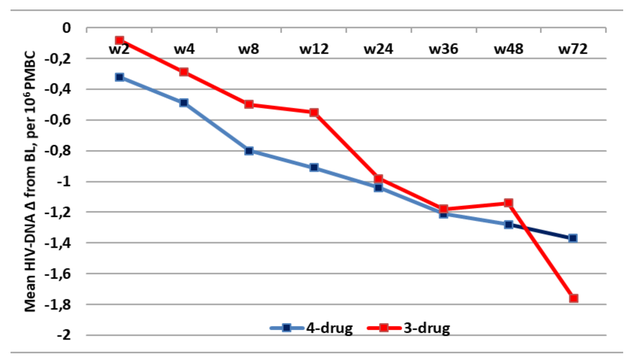
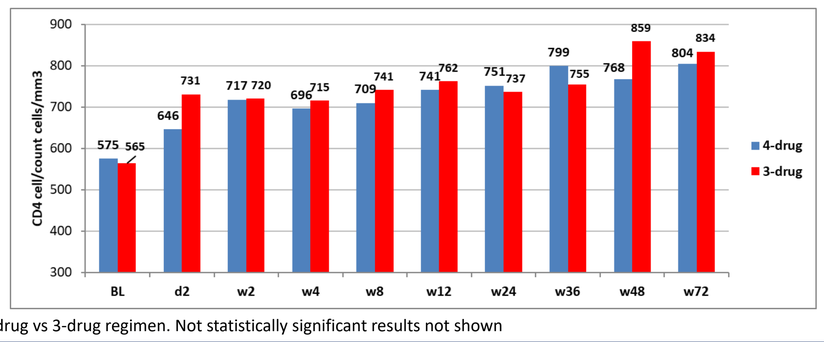


FIG 6: MEAN CD4 CELL COUNT AT SPECIFIC TIME POINTS ACCORDING TO TREATMENT GROUP



*4 drug vs 3-drug regimen. Not statistically significant results not shown

CONCLUSIONS:

In PHI, an intensified 4-drug regimen including RAL and DRV/b and a 3-drug DTG-based cART did show a comparable virological response.

Both strategies were associated with a **highly effective virological suppression**, proving to be **two valid and comparable treatment options for this stage of infection.**

The trend towards a better virological performance of 3-drug regimen, especially in patients with lower baseline viremia, was no longer confirmed after adjustment by adherence level as time-dependent co-variate, supporting **the role of adherence as possible limiting factor of 4-drug high-pill regimen.**