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Determinants and outcomes of the choice to switch to dolutegravir within different 3- or 2-drug regimens in a single-center cohort: the DOLUTILITY Study

The Dolutility Group

Restelli S [1], Romeri F [2], Piscaglia M [1], Rizzelli D [2], Gallazzi I [1], Paladini L [1], Cossu MV [1], Micheli V [2] and Capetti AF [1]

[1] 1st Division of Infectious Diseases, [2] Clinical Microbiology Unit, ASST Fatebenefratelli-Sacco, Milano

Background

Dolutegravir (DTG) was approved for antiretroviral therapy mainly on data from triple association with two nucleosides, however very soon physicians started to use it within different regimens, including two-drug regimens [1,2]. This analysis aims to investigate whether various DTG-based regimens have their own specificity and to describe them.

Methods

the DOLUTILITY Study is a single-center part of the ODOACRE Cohort. For all the patients who started DTG in any combination from November, 10, 2014, to April, 30, 2017, we collected baseline demographic, pharmacologic, virologic, immunologic and metabolic data, routine clinical data and blood work and outcomes. Only those subjects who had started DTG at least 96 weeks before the analysis (April, 30, 2016) were included. The statistical analysis is based on the Mann-Whitney test and the Wilcoxon test for continuous variables and on the Fisher exact test for contingency.

Results

1039 patients were included. The six regimens that were studied are: abacavir/ lamivudine/DTG (ABC/3TC/DTG), n = 614, DTG plus 3TC, n = 47, DTG plus rilpivirine (RPV), n = 132, DTG plus boosted darunavir (bDRV), n = 95, DTG plus boosted/unboosted atazanavir (b/uATV), n = 59, and DTG plus tenofovir/emtricitabine (TFV/FTC), n = 92. Table 1 summarizes the baseline demographic and epidemiologic characteristics. Overall, DTG+bDRV and DTG+TFV/FTC had longer time from HIV diagnosis and longer time on therapy (P< 0,0001 for both), while DTG+bDRV and DTG+RPV had more CDC stage C diagnosis and history of treatment failure (P< 0,0001 for both), DTG+RPV had often been chosen for concomitant treatment of HCV and HBV coinfection was present only in the DTG+TFV/FTC group. The analysis of past exposure to antiretrovirals and baseline and historical resistance-associated mutations (RAMs) revealed that DTG+bDRV and DTG+RPV had the heaviest burden, while DTG+3TC was only slightly affected. Table 2 describes the main reasons for the switch and their statistical relevance, compared to the choice for ABC/3TC/DTG. All the regimens showed >92% efficacy and the few viral failures (12 overall) were not accompanied by the selection of new mutations.

Conclusions

ABC/3TC/DTG being the main choice, DTG/3TC is the choice for subjects with cardiovascular risk, short drug experience and few or no mutations, DTG/RPV for drug-experience subjects who retain sensitivity to both drug and need such regimen to avoid or correct metabolic problems, DTG/bDRV is a regimen for salvage or simplification of salvage, while DTG/b/uATV and DTGTFV/FTC have intermediate profiles.

Introduction

Since the commercial availability of dolutegravir (DTG), perceiving it's antiretroviral potency, high genetic barrier to resistance and low metabolic impact, several physicians started to use it within and outside the clinical trials' schemes, generating a variety of antiretroviral regimens, fit for the variety of clinical situations and treatment history which characterize the HIV outpatients' population.

Camelia Gubavu was the first author to report such heterogeneity [3] and we followed with more structured multicentre observational studies, particularly focused on the associations of dolutegravir plus rilpivirine and of dolutegravir plus boosted darunavir as dual regimens in different settings.

With this analysis we mean to investigate how has dolutegravir been used in our center, if indeed different regimens are proposed to different types of subjects, how they are being tolerated and what is the level of efficacy.

Methods

All HIV-1 infected naïve subjects who had taken at least once from Luigi Sacco Hospital Pharmacy dolutegravir (either as Tivicay™ or as Triumeq™) between November 10, 2014 and April 30, 2017 were retrospectively included in an observational cohort. The list of subjects was obtained by the Pharmacy Unit and the relative case record forms were investigated gathering demographic, epidemiologic, clinical, pharmacological, immunovirological and metabolic data. For drug resistance, historical data have been gather to form an 'ever observed' mutation set.

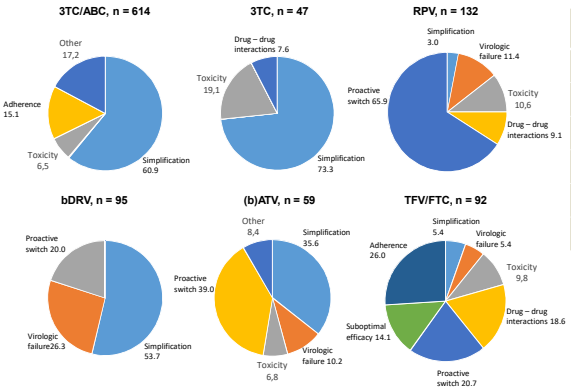
Data have been analysed by treatment cohorts (regimens) at 96 weeks of follow-up, with an accepted window of two months.

Fisher exact test and Odds ratio [CI95] were calculated for the different features. The population size was determined by the physicians' choices and by the time window.

Population

		ABC + 3TC (n. 614)	3TC (n. 47)	RPV (n. 132)	b/DRV (n. 95)	(b)ATV (n. 59)	TFV + FTC (n. 92)
Sex	M	485 (79%)	34 (72%)	85(64%)	61 (64%)	34 (58%)	73 (79%)
	F	128 (21%)	13 (28%)	47 (36%)	44 (36%)	25 (42%)	19 (21%)
Ethnicity	Caucasian	500 (81%)	42 (89.4%)	121 (91.7%)	80 (84.2%)	47 (79.7%)	82 (89.1%)
	African	35 (5.7%)	3 (6.4%)	9 (6.8%)	4 (4.2%)	5 (8.5%)	2 (2.2%)
	Asian	11 (1.8%)	2 (4.2%)	2 (1.5%)	/	/	1 (1.1%)
	Hispanic	67 (10.9%)	/	/	6 (6.3%)	6 (10.1%)	/
	Other	4 (0.6%)	/	/	5 (5.3%)	1 (1.7)	1 (1.1%)
Age		49.7	39±1	47±1	56.5	54.5±2.5	50,3±6,5
Risk factor	Heterosexual	215 (35%)	19 (40.5%)	46 (34.8%)	37 (38.9%)	22 (37.3%)	20 (21.6%)
	Homosexual	264 (43%)	20 (42.5%)	43 (32.7%)	19 (20%)	18 (30.5%)	35 (38.3%)
	Intravenous Drug User	129 (21%)	8 (17%)	41 (31%)	38 (40%)	19 (32.2%)	37 (40.1%)
	Other	6 (1%)	/	2 (1.5%)	1 (1.1%)	/	/

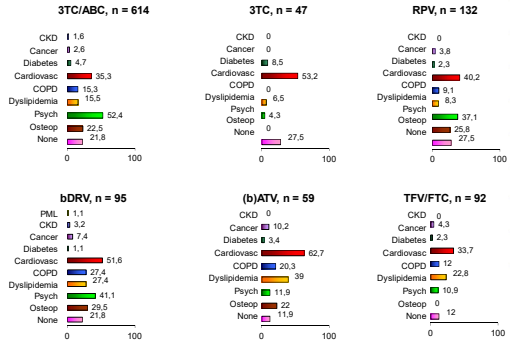
Main reason for switching therapy, %



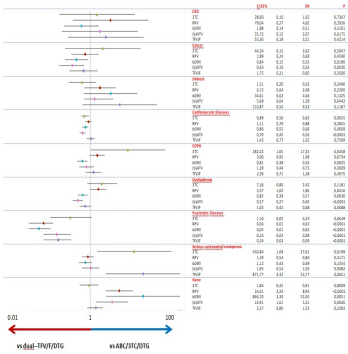
ABC/3TC vs	3TC	RPV	bDRV	(b)ATV	TFV/FTC
Simplification	P <0.0001	P <0.0001	P=0.26	P=0.0005	P <0.0001
Proactive	P <0.0001	P <0.0001	P <0.0001	P <0.0001	P <0.0001
Toxicity	P=0.0023	P=0.136	P <0.0001	P=1	P=0.269
Failure	P=0.6197	P =0.<0001	P <0.0001	P =0.009	P =0.176
Adherence	P =0.0008	P <0.0001	P <0.0001	P =0.0001	P =0.877
Drug-drug interactions	P <0.0001	P <0.0001	P=1	P=1	P <0.0001

Favours ABC/3TC · Favours RPV · Favours (b)ATV · Favours 3TC · Favours bDRV · Favours TFV/FTC

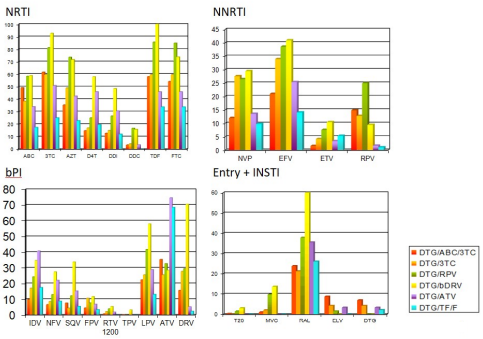
Comorbidities (%, total ≥ 100)



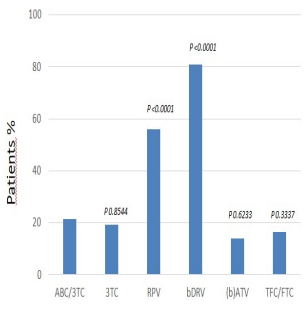
Comorbidities (OR, IC95)



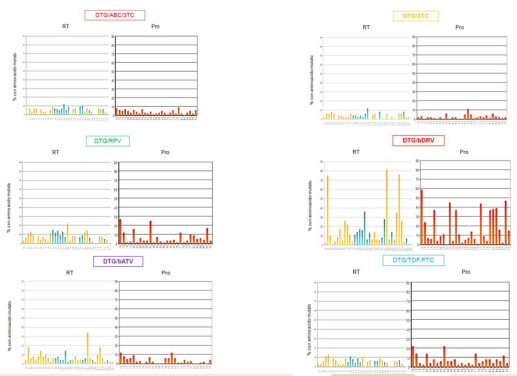
Past exposure to antiretrovirals



Past viral failures (compared to ABC/3TC)



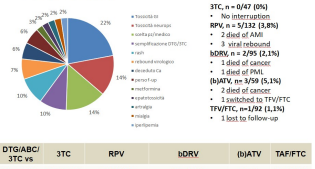
Baseline Resistance-Associated Mutations



Immunologic and virologic outcomes

	Zenith HIV RNA	Baseline viral suppression	96 w HIV RNA < 50 copies/mL (ITT: M=F)	Viral failures	Stop DTG
ABC/3TC	99.725	98 %	92,8 %	3 (0,5%)	41 (6,7%)
3TC	95.700	100%	97,9 %	1 (2,1%)	/
RPV	105.260	88,6 %	96,2 %	3 (2,3%)	5 (3,8)
bDRV	201.000	73,7 %	94,7 %	3 (3,1%)	2 (2,1%)
(b)ATV	81.656	94,6 %	93,2 %	1 (1,7%)	3 (5,1%)
TDF/FTC	245.897	94,6 %	97,8 %	1 (1,1%)	1 (1,1%)

Reasons for stopping therapy



DTG/ABC/3TC vs	3TC	RPV	bDRV	(b)ATV	TAF/FTC
Stop DTG	P = 0.106	P = 0.316	P = 0.104	P = 1	P = 0.032

Conclusions:

Triple	ABC/3TC	Lower incidence of neuropsychic AEs compared to the literature	Dual	3TC	Very promising in simplification from triple therapies in subjects without drug resistance (TANGO trial ongoing)
	TFV/FTC	Slightly better potency vs. DTG/ABC/3TC Fit for subject coinfected with HBV.		RPV	Effective also as proactive switch , the only limitation compared to the SWORD study appears to be full sensitivity to the regimen drugs
				bDRV	Appealing strategy for salvage or simplification of salvage regimens.
				(b)ATV	More complex to find the best population, probably simplification or NRTI-sparing for subjects already taking ATV

References

1. Capetti AF, Cossu MV, Paladini L and Rizzardini G. Dolutegravir plus rilpivirine dual therapy in treating HIV-1 infection. Exp. Opin. Pharmacother. DOI: 10/1080/14656566.2017.1417984. Epub 2017 Dec 22.
2. Maggiolo F, Gulminetti R, Pagnucco L, Digaetano M, Benatti S, Valenti D, Callegaro A, Ripamonti D, Mussini C. Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. BMC Infect Dis. 2017 Mar 16;17(1):215.
3. Gubavu C, Prazuck T, Niang M, Buret J, Mille C, Guinard J, Avettand-Fenoel V, Hocqueloux L. Dolutegravir-based monotherapy or dual therapy maintains a high proportion of viral suppression even in highly experienced HIV-1-infected patients. J Antimicrob Chemother. 2016 Apr;71(4):1046-50.