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Background

Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), is currently recommended for treatment initiation in antiretroviral-naïve by most of clinical guidelines. Data from randomized trials demonstrated superiority of DTG over NNRTI and PI/r, supporting its clinical use especially in first-line regimens with high-viral load, regardless of the NRTI-pair (TDF/FTC or ABC/3TC) used in combination. Data on patterns of indication for use of DTG in clinical practice are scarce and determinants of its initiation not fully understood.

Objectives

Aim of this analysis was to describe DTG use as first-line regimen in a representative unselected ART-naïve population in Italy and to identify its determinants and patterns of prescription.

Methods

All patients enrolled in Icona Foundation Cohort Study, starting a DTG-based regimen from ART-naïve, and those concomitantly starting other third drugs (control group) after Jan 01, 2014 were included. The analysis was restricted to participants who started with the NRTI-pair of TDF/FTC or ABC/3TC. A cross-sectional analysis was performed comparing demographics, clinical and lifestyle factors measured at the time of starting cART in DTG-based regimens vs. control regimens using chi-square for categorical and Wilcoxon test for continuous variables. Univariable and multivariable logistic regression was performed to identify predictors of DTG initiation. The hypothesis that there was a differential use of the NRTI-pair in DTG vs. controls according to pre-cART viral load levels was formally tested by including an interaction term in the model.

Table 1. General characteristics of the study population according to treatment started

Characteristics	Treatment groups			Total
	DTG-based N= 415	Control N= 2,307	p-value*	
Gender, n(%)			0.613	
Female	79 (19.0%)	464 (20.1%)		543 (19.9%)
Age, years			0.033	
Median (IQR)	40 (31, 48)	38 (30, 46)		38 (30, 47)
Mode of HIV Transmission, n(%)			0.018	
IDU	21 (5.1%)	137 (6.0%)		158 (5.9%)
Homosexual contacts	206 (50.5%)	1,092 (47.9%)		1,298 (48.3%)
Heterosexual contacts	137 (33.0%)	890 (38.6%)		1,027 (37.7%)
Other/Unknown	44 (10.8%)	160 (7.0%)		204 (7.6%)
Nationality, n(%)			0.135	
Not Italian	82 (19.8%)	548 (23.8%)		630 (23.1%)
HBSAg, n(%)			<.001	
Negative	253 (61.0%)	1,643 (71.2%)		1,896 (69.7%)
Positive	0 (0.0%)	4 (0.2%)		4 (0.1%)
Not reported	162 (39.0%)	660 (28.6%)		822 (30.2%)
HCVAb, n(%)			<.001	
Negative	248 (59.8%)	1,581 (68.5%)		1,829 (67.2%)
Positive	9 (2.2%)	117 (5.1%)		126 (4.6%)
Not reported	158 (38.1%)	609 (26.4%)		767 (28.2%)
AIDS diagnosis, n(%)			0.032	
Yes	57 (13.7%)	235 (10.2%)		292 (10.7%)
CD4 count, cells/mm³			0.010	
Median (IQR)	350 (120, 565)	395 (230, 545)		390 (209, 548)
CD4 count nadir, cells/mm³			0.002	
Median (IQR)	327 (117, 537)	383 (224, 514)		375 (203, 519)
CD4 count			0.005	
<=200 cells/mm ³	115 (34.7%)	688 (29.8%)		803 (24.3%)
CD8 count, cells/mm³			0.656	
Median (IQR)	854 (566, 1166)	932 (637, 1316)		922 (622, 1297)
CD4/CD8 ratio			0.001	
<=0.3	130 (43.4%)	772 (45.0%)		903 (44.8%)
Viral load**, log₁₀ copies/mL			0.001	
Median (IQR)	4.68 (4.06, 5.30)	4.54 (3.86, 5.09)		4.57 (3.90, 5.11)
Time from HIV diagnosis to baseline, months			<.001	
Median (IQR)	1 (1, 5)	3 (1, 21)		2 (1, 18)
Time in follow-up, months			<.001	
Median (IQR)	2 (0, 8)	10 (3, 18)		9 (2, 17)
Diabetes, n(%)			0.205	
Yes	11 (2.7%)	40 (1.7%)		51 (1.9%)
Smoking, n(%)			<.001	
No	134 (32.3%)	962 (41.7%)		1,096 (40.3%)
Yes	122 (29.4%)	771 (33.4%)		893 (32.8%)
Unknown	159 (38.3%)	574 (24.9%)		733 (26.9%)
Total cholesterol, mg/dL			0.070	
Median (IQR)	157 (130, 182)	162 (139, 186)		161 (138, 186)
HDL cholesterol, mg/dL			0.971	
Median (IQR)	40 (35, 49)	41 (33, 49)		41 (33, 49)
eGFR (CKD-Epi formula), ml/min/1.73m²			0.726	
Median (IQR)	107.7 (94.58, 117.2)	107.8 (95.72, 117.8)		107.8 (95.61, 117.8)
NRTI-pair started(%)			<.001	
TDF+FTC	220 (53.0%)	2103 (91.2%)		2323 (85.3%)
ABC+3TC	195 (47.0%)	204 (8.8%)		399 (14.7%)
Third drug started, n(%)				
Efavirenz	0 (0.0%)	144 (6.2%)		144 (5.3%)
Nevirapine	0 (0.0%)	8 (0.3%)		8 (0.3%)
Rilpivirine	0 (0.0%)	776 (33.6%)		776 (28.5%)
Liponavir/r	0 (0.0%)	27 (1.2%)		27 (1.0%)
Atazanavir/r	0 (0.0%)	205 (8.9%)		205 (7.5%)
Darunavir/r	0 (0.0%)	444 (19.2%)		444 (16.3%)
Raltegravir	0 (0.0%)	197 (8.5%)		197 (7.2%)
Dolutegravir	415 (100%)	0 (0.0%)		415 (15.6%)
Site geographical position, n(%)			<.001	
North	269 (64.8%)	1,239 (53.7%)		1,508 (55.4%)
Center	100 (24.1%)	866 (37.5%)		966 (35.5%)
South	46 (11.1%)	202 (8.8%)		248 (9.1%)
Calendar year of baseline**			<.001	
Median (IQR)	2015 (2015, 2016)	2015 (2014, 2015)		2015 (2014, 2015)

*Chi-square or Wilcoxon test as appropriate
**Stratification factor

Results

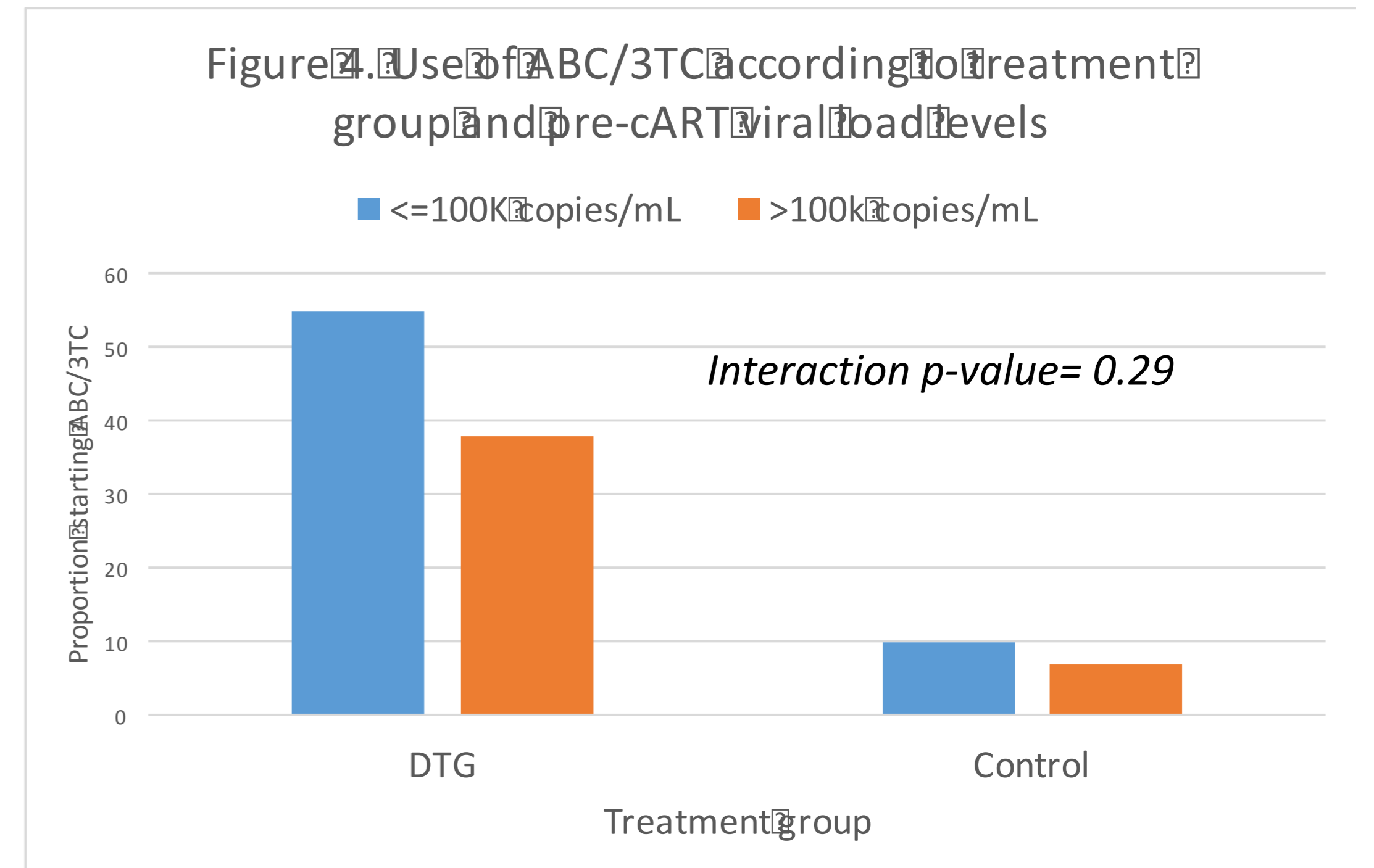
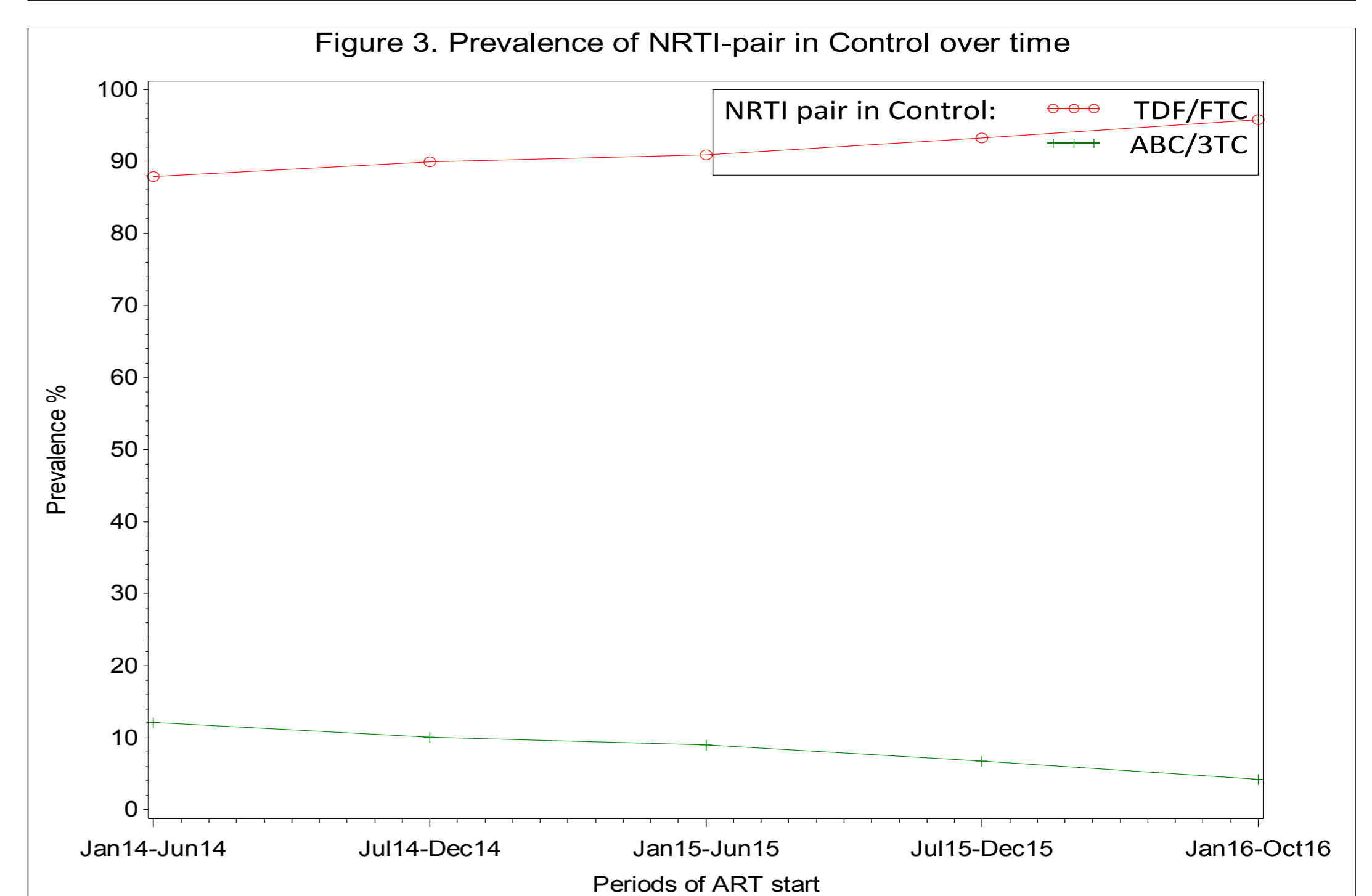
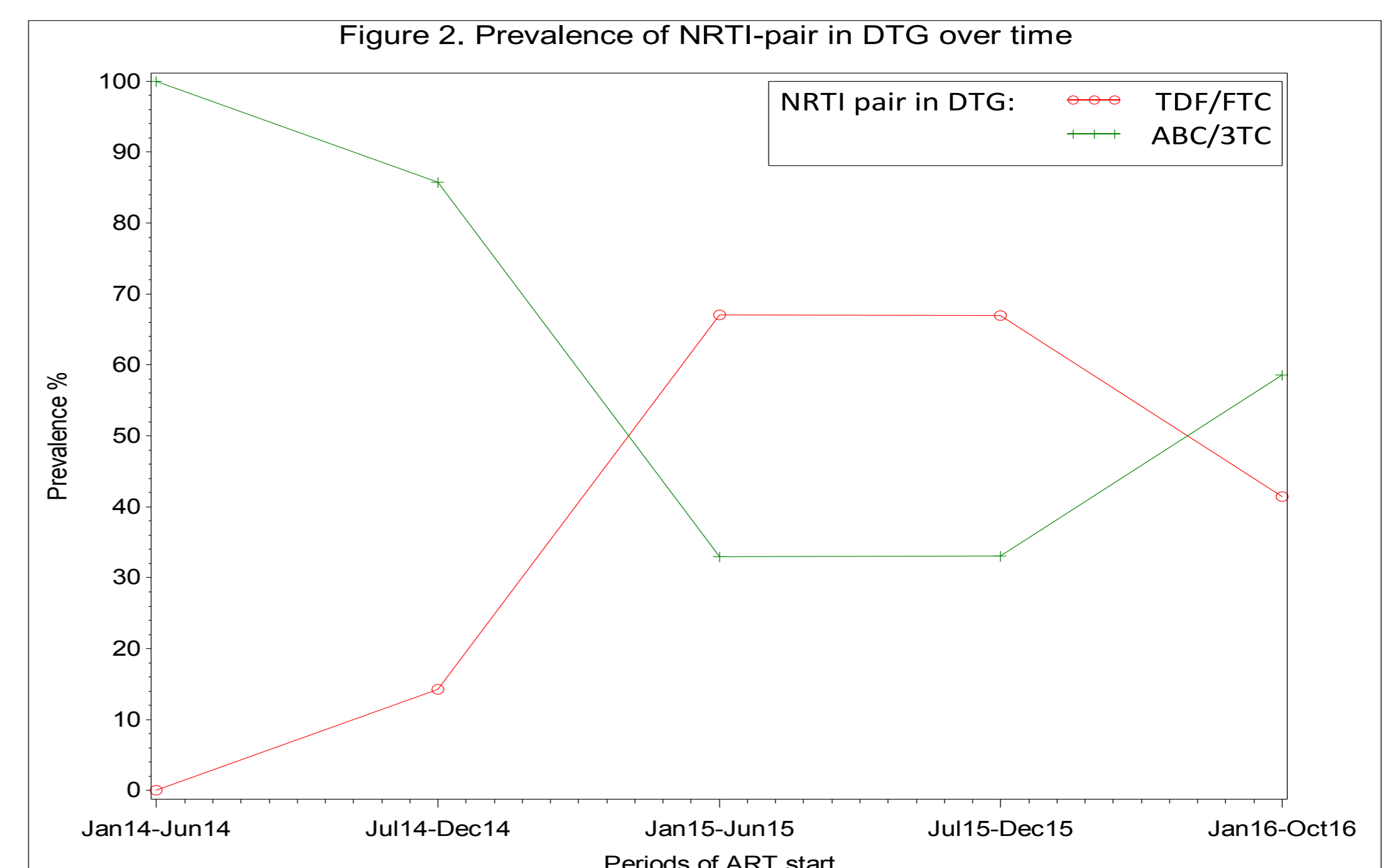
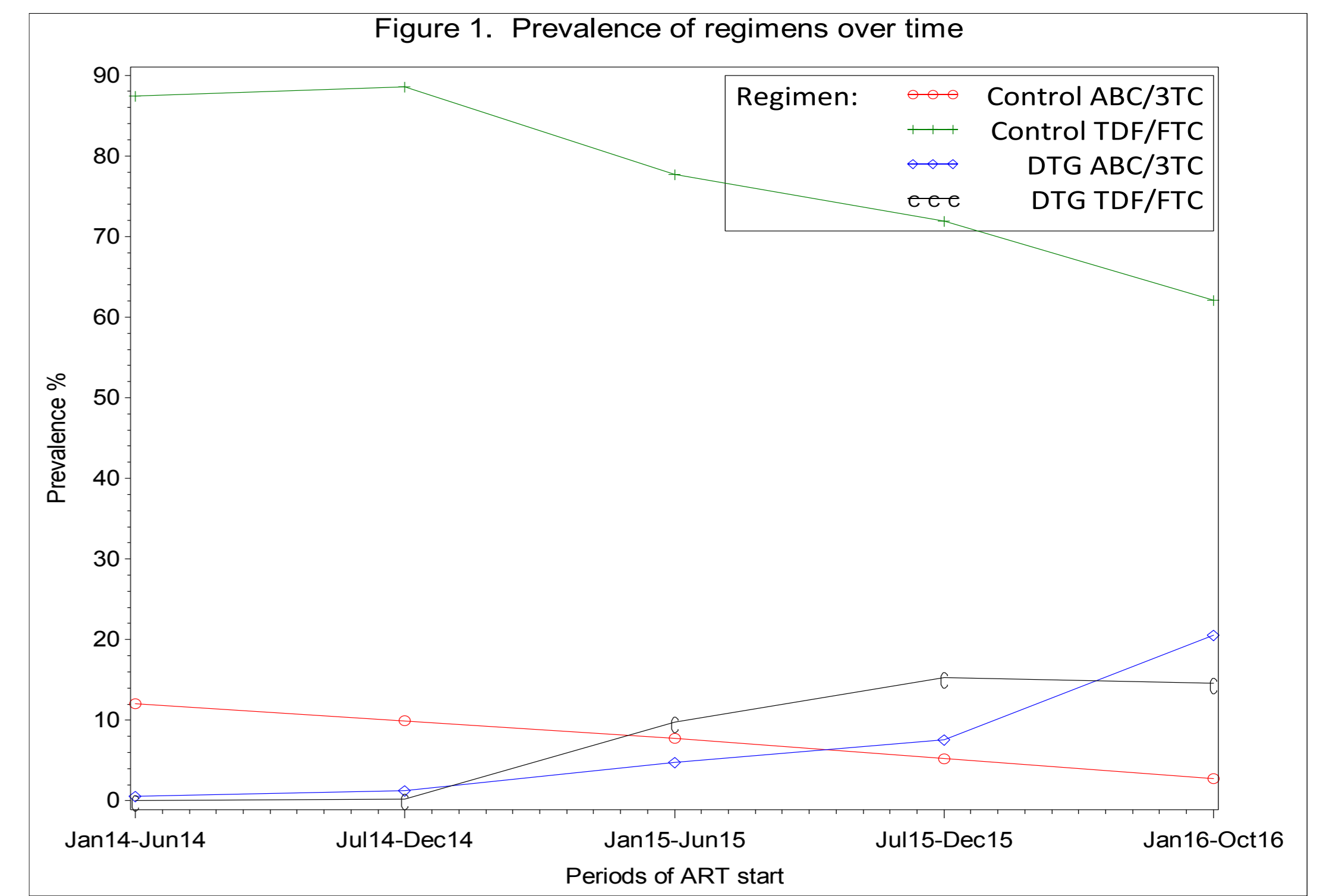
A total of 2,722 ARV-naïve individuals starting cART were included (DTG=415; NNRTI=931; PI/r=647; other INSTI=729). Over the period of enrolment studied, DTG was initiated as part of their first-line regimen by 15% of the participants in the cohort.

General characteristics of patients enrolled according to treatment started are shown in Table 1. DTG was more frequently prescribed in older participants, MSM, people with AIDS diagnosis, low CD4 count and high plasma VL.

In Figures 1-4, trends of prescription pattern of DTG and controls by NRTI backbone over time are reported.

Table 2. Odds ratios of starting DTG vs. control from fitting a logistic regression model

Characteristic	Odds ratios of starting Dolutegravir vs. Control			
	Unadjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
Gender, n(%)				
Female vs. male	0.93 (0.72, 1.22)	0.613	0.57 (0.27, 1.21)	0.142
Age, years				
per 10 years older	1.10 (1.01, 1.21)	0.036		
Mode of HIV Transmission, n(%)				
IDU	1.00			
Homosexual contacts	1.23 (0.76, 1.99)	0.399		
Heterosexual contacts	1.00 (0.61, 1.64)	0.987		
Other/Unknown	1.79 (1.02, 3.17)	0.044		
Nationality, n(%)				
Not Italian vs. Italian	0.79 (0.61, 1.03)	0.076	0.60 (0.30, 1.20)	0.150
AIDS diagnosis, n(%)				
Yes vs. No	1.40 (1.03, 1.92)	0.032		
HCVAb, n(%)				
Negative	1.00			
Positive	0.49 (0.25, 0.98)	0.043		
Not tested	1.65 (1.33, 2.06)	<.001		
CD4 count, cells/mm³				
per 100 cells higher	0.94 (0.90, 0.98)	0.009	0.98 (0.89, 1.07)	0.646
CD4 count nadir, cells/mm³				
per 100 cells higher	0.94 (0.90, 0.99)	0.023		
CD8 count, cells/mm³				
per 100 cells higher	0.97 (0.95, 1.00)	0.021		
Viral load, log₁₀ copies/mL				
>100k vs. <=100k	1.45 (1.14, 1.85)	0.003	1.67 (0.93, 3.03)	0.088
Diabetes, n(%)				
Yes vs. No	1.54 (0.79, 3.04)	0.207		
Smoking, n(%)				
No	1.00		1.00	
Yes	1.14 (0.87, 1.48)	0.342	1.07 (0.62, 1.85)	0.812
Unknown	1.99 (1.55, 2.56)	<.001	0.91 (0.45, 1.85)	0.802
Total cholesterol, mg/dL				
per 10 higher	0.65 (0.41, 1.02)	0.064		
HDL cholesterol, mg/dL				
per 10 higher	0.79 (0.25, 2.49)	0.693	2.42 (0.44, 13.30)	0.309
Time from HIV diagnosis to date of starting cART				
per year longer	0.90 (0.86, 0.95)	<.001	0.89 (0.81, 0.97)	0.007
e-GFR (CKD-Epi formula), ml/min/1.73m²				
per 60 higher	1.01 (0.95, 1.07)	0.801		
Blood glucose, mg/dL				
per 100 higher	1.39 (0.86, 2.26)	0.180		
Site geographical position, n(%)				
North	1.00		1.00	
Center	0.53 (0.42, 0.68)	<.001	0.43 (0.23, 0.80)	0.007
South	1.05 (0.74, 1.48)	0.787	1.41 (0.74, 2.68)	0.301
NRTI pair				
ABC/3TC vs. TDF/3TC	9.14 (7.18, 11.62)	<.001	21.62 (12.62, 37.01)	<.001
Period of initiation				
Jan-Dec 2014	1.00		1.00	
Jan-Dec 2015	22.38 (11.79, 42.48)	<.001	20.81 (8.22, 52.70)	<.001
Jan-Oct 2016	55.21 (28.96, 105.3)	<.001	53.71 (20.48, 140.9)	<.001



Conclusions/Limitations

- Over the first 32 months after its introduction in first-line treatment in Italy, there was a clear increase of DTG prescriptions over time.
- Patterns of prescription were close to those observed for control regimens, except for a less frequent initiation of DTG in people with a longer time from HIV diagnosis to the date of cART, a more frequent initiation in clinical sites located in the north of the country as compared to central regions, and a trend towards an increased probability of DTG starting in patients with high-VL baseline level.
- ABC/3TC was significantly more frequently prescribed with DTG than with control drugs, although there was no evidence that this was more so at low VL
- Concerns on ABC effects and lack of rapid HLA results might have affected clinicians choices about NRTI backbone selection, but is a non testable assumption.

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