From naive to highly treated subjects. Efficacy of cART

N. prog: OC 65

Title: **Viral potency and durability of emtricitabine/tenofovir alafenamide (F/TAF) based regimens in the real life setting**

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Abstract body
Background: F/TAF has been recently introduced in the antiretroviral setting based on randomized trials showing a comparable efficacy to that of F/tenofovir disoproxil fumarate (TDF) with greater kidney and bone safety. Nevertheless, information regarding TAF-based regimens in the real world setting is still lacking.
Material and methods: We included ART-naïve patients enrolled in the ICONA cohort who started TAF-based regimens as first line as well as those enrolled in a parallel cohort constructed ad hoc to include patients who were switched to a TAF-based regimen with a HIV RNA ≤50 copies/mL. All consecutive patients who started or were switched to an F/TAF-including regimen over 2015 to 2017 were included. Time to discontinuation for any cause, for toxicity or for treatment failure (TF) (confirmed HIV RNA >50 copies/mL after six months or discontinuation for any cause) were estimated by Kaplan-Meier curves. Cox regression models were used to identify independent predictors of the same outcomes, separately in the two groups.
Results: 2,137 patients were included; 381 ART-naïve starting an F/TAF regimen and 1,756 ART-experienced (ART-exp) who switched to an F/TAF regimen with stable viral suppression. Table 1 shows baseline characteristics of the enrolled population. The more frequently used combined regimens were E/C/F/TAF (41% naïve; 38% switched), DTG+F/TAF (30%; 7%), R/F/TAF (10%; 33%), D/C/F/TAF (10%; 7%). Among the ART-exp group, 1,288 had never previously failed ART while 468 had experienced virological failure to ≥1 regimen. Median duration of viral suppression at switching was 41 months (IQR 23, 72). In the ART-naïve group, the 1-year risk of discontinuing F/TAF was 8.1% (95% CI 5.1%-11.0%) for any causes and 2.5% (0.8%-4.3%) for toxicity, while the 1-year probability of TF was 10.4% (6.8%-13.9%). In the ART-exp group, the 1-year risks were estimated at 5.0% (95% CI 2.2%-7.7%), 0.6% (0.2%-1.0%) and 5.4% (3.5%-7.3%) for discontinuation for any cause, for toxicity and TF, respectively. In the ART-naïve group, by multivariable Cox regression, HCV coinfection was associated with an increased risk of discontinuation, and higher baseline VL with an increased risk of TF. In the ART-exp group, a more recent calendar year and a history of ART interruption due to toxicity were independently associated with a lower risk of TF, whereas a history of previous virologic failure was associated with higher risk (Table 2).
Conclusions: In our cohort, F/TAF-based regimens initiated for the first time demonstrated high efficacy and a low rate of discontinuation, both in the ART-naïve and in the ART-experienced population. Reduced risk of discontinuation or failure in more recent calendars year may coincide with a switch over time to F/TAF in combination with increasingly safer and more effective drugs. In the ART-experienced

population, history of virologic failure and reasons for stopping previous regimens should be considered to identify people at higher risk of failing therapy.
This study is supported by a grant from Gilead International

Table1. Main characteristics of 2,137 patients receiving F/TAF according to naïve or treated status.

	ART history			
Characteristics	**ART-naive**	**ART treated**	**p-value***	**Total**
	N= 381	**N= 1756**		**N= 2137**
Gender, n(%)			0.351	
Female	58 (15.2%)	302 (17.2%)		360 (16.8%)
Mode of HIV Transmission, n(%)			0.031	
IDU	16 (4.3%)	147 (8.4%)		163 (7.7%)
Homosexual contact	202 (53.9%)	846 (48.6%)		1048 (49.5%)
Heterosexual contact	138 (36.2%)	653 (37.2%)		791 (37.0%)
Other/Unknown	19 (5.1%)	96 (5.5%)		115 (5.4%)
Nationality, n(%)			<.001	
Not Italian	95 (24.9%)	287 (16.3%)		382 (17.9%)
AIDS diagnosis, n(%)			<.001	
Yes	20 (5.2%)	229 (13.0%)		249 (11.7%)
CVD diagnosis, n(%)			0.289	
Yes	3 (0.8%)	26 (1.5%)		29 (1.4%)
HBsAg, n(%)			<.001	
Negative	308 (80.8%)	1475 (84.0%)		1783 (83.4%)
Positive	1 (0.3%)	73 (4.2%)		74 (3.5%)
Not tested	72 (18.9%)	208 (11.8%)		280 (13.1%)
HCV Ab, n(%)			<.001	
Negative	296 (77.7%)	1418 (80.8%)		1714 (80.2%)
Positive	15 (3.9%)	190 (10.8%)		205 (9.6%)
Not tested	70 (18.4%)	148 (8.4%)		218 (10.2%)
*Calendar year of baseline***			<.001	
Median (IQR)	2017 (2017, 2018)	2017 (2017, 2017)		2017 (2017, 2017)
2009-2014	0 (0.0%)	0 (0.0%)		0 (0.0%)
2015	2 (0.5%)	3 (0.2%)		5 (0.2%)
2016-2017	379 (99.5%)	1753 (99.8%)		2132 (99.8%)
Age, years			<.001	
Median (IQR)	39 (31, 48)	45 (37, 53)		44 (36, 52)
CD4 count, cells/mmc			<.001	
Median (IQR)	355 (152, 546)	684 (498, 886)		627 (422, 842)
<=200 cells/mmc	105 (28.3%)	53 (3.0%)	<.001	158 (7.4%)
CD4 count nadir, cells/mmc			0.001	
Median (IQR)	346 (150, 530)	298 (162, 427)		302 (161, 445)
CD8 count, cells/mmc			0.031	
Median (IQR)	870 (603, 1261)	817 (607, 1095)		826 (606, 1111)
Viral load, log10 copies/mL			<.001	
Median (IQR)	4.74 (4.21, 5.42)	0.00 (0.00, 1.56)		1.11 (0.00, 1.59)
<=50 copies/mL, n(%)	0 (0.0%)	1756 (100.0%)	<.001	1756 (82.5%)
>100,000 copies/mL, n(%)	155 (41.7%)	0 (0.0%)	<.001	155 (7.3%)
egfr (CKD_Epi formula), ml/min/1.73m²			<.001	
Median (IQR)	106.2 (92.09, 116.6)	88.90 (76.00, 102.1)		91.65 (77.64, 105.4)
Below 60, n(%)	9 (2.5%)	119 (6.8%)	0.002	128 (6.0%)
Site geographical position, n(%)			<.001	
North	223 (58.5%)	1255 (71.5%)		1478 (69.2%)
Center	123 (32.3%)	399 (22.7%)		522 (24.4%)
South	35 (9.2%)	102 (5.8%)		137 (6.4%)

Diabetes, n(%)			0.009	
Yes	5 (1.3%)	71 (4.0%)		76 (3.6%)
Smoking, n(%)			<.001	
No	112 (29.4%)	870 (49.5%)		982 (46.0%)
Yes	105 (27.6%)	687 (39.1%)		792 (37.1%)
Unknown	164 (43.0%)	199 (11.3%)		363 (17.0%)
Total cholesterol, mg/dL			<.001	
Median (IQR)	161 (136, 188)	177 (153, 201)		175 (150, 199)
HDL cholesterol, mg/dL			<.001	
Median (IQR)	40 (33, 48)	46 (38, 54)		45 (37, 53)
Use of statins, n(%)			<.001	
Yes	4 (1.0%)	206 (11.7%)		210 (9.8%)
Use of blood pressure lowering drugs, n(%)			<.001	
Yes	15 (3.9%)	203 (11.6%)		218 (10.2%)
Time from HIV diagnosis to date of starting cART, months			<.001	
Median (IQR)	1 (1, 2)	67 (33, 122)		53 (19, 108)
Blood glucose, mg/dL			0.026	
Median (IQR)	86 (79, 93)	87 (81, 95)		87 (81, 95)
Type of regimen started, n(%)			<.001	
Dual	2 (0.5%)	6 (0.3%)		8 (0.4%)
Triple	363 (95.3%)	1732 (98.6%)		2095 (98.0%)
Four or more	16 (4.2%)	18 (1.0%)		34 (1.6%)
Education, n(%)			0.004	
Primary school	8 (2.1%)	53 (3.0%)		61 (2.9%)
Secondary school	46 (12.1%)	347 (19.8%)		393 (18.4%)
College	89 (23.4%)	548 (31.2%)		637 (29.8%)
University	64 (16.8%)	230 (13.1%)		294 (13.8%)
Other/Unknown	174 (45.7%)	578 (32.9%)		752 (35.2%)
Employment, n(%)			<.001	
Unemployed	37 (13.5%)	162 (11.2%)		199 (11.6%)
Employed	144 (52.4%)	804 (55.6%)		948 (55.1%)
Self-employed	42 (15.3%)	256 (17.7%)		298 (17.3%)
Occasional	5 (1.8%)	42 (2.9%)		47 (2.7%)
Student	20 (7.3%)	42 (2.9%)		62 (3.6%)
Retired	14 (5.1%)	39 (2.7%)		53 (3.1%)
Invalid	0 (0.0%)	2 (0.1%)		2 (0.1%)
Housewife	3 (1.1%)	38 (2.6%)		41 (2.4%)
Other/unknown	10 (3.6%)	62 (4.3%)		72 (4.2%)
Follow-up time, months			<.001	
Median (IQR)	8 (4, 12)	10 (6, 13)		10 (6, 13)

*Chi-square or Kruskal-Wallis test as appropriate

Table 2. Relative hazards of discontinuing F/TAF for any cause, for toxicity or having a treatment failure (TF) as combined and point from fitting Cox regression models according to ART history.

	Adjusted* RH (95% CI) of discontinuation for any cause	**p-value**	**Adjusted* RH (95% CI) of discontinuation for toxicity**	**p-value**	**Adjusted* RH (95% CI) of TF****	**p-value**
ART-naive						
HCV coinfection						
No	1.00		1.00			
Yes	8.27 (1,46, 46,9)	0.017	47.6 (1.47, 1545.0)	0.03		
Viral load, log_{10} copies/mL						
per log higher					1.49 (1.00, 2.23)	0.049
ART-experienced						
Calendar year of baseline						
per more recent	n.d.^		n.d.^	-	0.40 (0.21, 0.76)	0.005
Reason for stopping previous regimen						
Other	n.d.^		n.d.^	-	1.00	0.057
Toxicity					0.40 (0.16, 1.03)	
History of virological failure						
No	n.d.^		n.d.^	-	1.00	<0.001
Yes					2.80 (1.59, 4.93)	

*In patients naïve, adjusted for: gender, mode of HIV transmission, AIDS diagnosis, HCV co-infection, age, nationality, CD4 count and VL at baseline, boosted regimen combined;
In patients who switched during VL suppression, adjusted for: gender, mode of HIV transmission, AIDS diagnosis, HCV co-infection, age, nationality, CD4 count and VL at baseline, number of previous regimes, reason for stopping previous regimen, history of VF, ART duration, viral suppression duration.
** Treatment failure (TF) definition: VL >50 copies/mL after 6 months from F/TAF initiation or discontinuation for any cause at any time of follow-up.
^ not estimable for very poor number of event.