Two years of exposure to elvitegravir/cobicistat/emtricitabine/tenofovir (E/C/FTC/TDF): an overview of the trend in laboratory parameters in clinical practice

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BACKGROUND

Despite a highly desirable rate of immuno-virological success, a decrease in eGFR (-14 ml/min) and a mild increase in lipids (+17 mg/dL total cholesterol) by 3 years from starting the combination elvitegravir/cobicistat/emtricitabine/tenofovir (E/C/FTC/TDF) was observed in persons living with HIV (PLWH) enrolled in clinical trials. Similar data from PLWH routinely seen for care are less frequently reported. Randomised studies have also shown an improvement of markers of kidney function in people switching from E/C/FTC/TDF to E/C/FTC/tenofovir alafenamide (TAF).

OBJECTIVES

- To describe the trajectories of main lipids, liver and kidney function markers in PLWH over a period of 2 years of exposure to E/C/FTC/TDF in a real-life setting.
- To identify people with faster eGFR deterioration who might need to be closely monitored in the view of a switch to E/C/FTC/TAF.

METHODS

We included PLWH attending clinics of Icona Network who received E/C/FTC/TDF for the first time and for whom there was ≥1 measure of eGFR (CKD-Epi) ALT and lipids (total cholesterol [T-c], LDL cholesterol [LDL-c], HDL cholesterol [HDL-c] and triglycerides) after enrolment. Fractional polynomials were used to describe population trajectories. Linear mixed models with random intercept/slope were fitted to identify factors associated with the slope, after adjusting for selected potential confounding factors in intercept (all shown in Table 2). Participants' follow-up was censored at date of starting lowering lipids treatment.

RESULTS

We studied 1,011 PLWH who started E/C/FTC/TDF (62% from ART-naïve), on average in the year 2015.

One hundred and ninety-six (19%) female, median age (IQR) 40 years (33-48), CD4 count 467 cells/mm³ (280-685), HIV-RNA 2.5 log₁₀ copies/mL (1.4-4.6). Ten participants (1%) started E/C/FTC/TDF with a eGFR <60 ml/min, 33 (3%) with a value <70 ml/min; other participants' characteristics at the time of starting E/C/FTC/TDF are shown in Table 1 A/B.

There was a decrease over time in mean level of eGFR (-6.4, 95% CI:[-7.4;-5.5] ml/min/year) and an increase in HDL-c (+1.3, [+2.4;+3.8] mg/dl/year), LDL-c (+4.7; [+2.9;+6.6] mg/dl/year) and T-c (+8.1, [+5.9;+10.4] mg/dl). In contrast, triglycerides (-1.2, [-5.6; +3.2] mg/dl/year) and ALT (+0.3, [-6.3;+7.0] UI/ml/year) showed a more stable trend (Figure 1).

By 2 years of exposure to E/C/FTC/TDF, median (IQR) values were 94 (80-105) ml/min for eGFR (3% had a value <60 ml/min), 113 (79-157) mg/dl for triglycerides, 110 (96-125) mg/dl for LDL-c and 178 (164-195) mg/dL for T-c.

There was evidence of a faster decline in eGFR in people who started E/C/FTC/TDF after 2015 (-8.8; 95% CI:[-11.8; -5.9] ml/min/year vs. 2010-2015; p<.001) and those starting from ART-naïve (-3.6, [-5.7; -1.5] ml/min/year vs. ART-treated, p<.001) (Table 2, panel A). More recent initiations showed higher baseline eGFR levels (103.4 vs. 99.2 min/ml, p<.001) which might partly explain the finding. Results were similar after excluding PLWH with baseline eGFR <70 min/ml.

ART-naïve participants (+11.4, [+6.1, +16.6] mg/dl/year vs. ART-treated, p<.001), those with a CD4 count of 0-200 (+8.5, [+0.2, +16.9] mg/dl/year vs. CD4 count >200, p<.001) and those with a HIV-RNA>100,000 copies/mL (+12.5, [+5.1, +19.9] mg/dl/year vs. HIV-RNA 0-100,000 copies/mL, p<.001) showed a higher increase in T-c (Table 2, panel B).

LIMITATIONS

- A linear model was used for convenience despite some of the trajectories seemed to deviate from a linear trend in the unit scale used.
- Only a, chosen *a priori*, limited number of biomarkers and exposures at time of E/C/FTC/TDF have been investigated.
- Although statistically significant, some of the found differences were small with possible little clinical implications.
- The ART-experienced group is likely to be a selected population with stable eGFR on a previous regimen already containing TDF.

CONCLUSIONS

- *Severe kidney or liver function and lipids abnormalities were seen in a very small proportion of our study population.*
- *Evolution of kidney and liver functions as well as of lipids levels was similar to that seen in clinical trials: alterations were limited and not clinically meaningful in most participants.*
- *However, ART-naïve PLWH are likely to experience faster eGFR decrease than that of the ART-treated population and they should be closely monitored to allow a prompt switch towards TAF-based regimens.*

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Table 1 – Main characteristics of the study population at initiation of E/C/FTC/TDF according to treatment history

A) Demographics

A) Demographics	ART-treated N= 383	ART-naïve N= 628	p-value	Total N= 1011
Gender, n(%)			0.016	
Female	89 (23.2%)	107 (17.0%)		196 (19.4%)
Mode of HIV Transmission, n(%)			0.003	
IDU	27 (7.1%)	29 (4.7%)		56 (5.6%)
Homosexual contacts	164 (43.3%)	343 (55.1%)		507 (50.6%)
Heterosexual contacts	161 (42.0%)	214 (34.1%)		375 (37.1%)
Other/Unknown	27 (7.1%)	36 (5.8%)		63 (6.3%)
Nationality, n(%)			0.098	
Not Italian	71 (18.5%)	144 (22.9%)		215 (21.3%)
AIDS diagnosis, n(%)			<.001	
Yes	66 (17.2%)	45 (7.2%)		111 (11.0%)
HCVAb, n(%)			<.001	
Negative	305 (79.6%)	465 (74.0%)		770 (76.2%)
Positive	43 (11.2%)	39 (6.2%)		82 (8.1%)
Not tested	35 (9.1%)	124 (19.7%)		159 (15.7%)
Calendar year of starting E/C/FTC/TDF			<.001	
Median (IQR)	2015 (2015, 2016)	2015 (2015, 2016)		2015 (2015, 2016)
Age, years			<.001	
Median (IQR)	43 (36, 50)	38 (31, 47)		40 (33, 48)
CD4 count, cells/mmc			<.001	
Median (IQR)	574 (385, 788)	389 (226, 570)		466 (280, 685)

B) Markers

B) Markers	ART-treated N= 383	ART-naïve N= 628	p-value	Total N= 1011
HIV-RNA, log10 copies/mL			<.001	
Median (IQR)	1.57 (1.08, 1.74)	4.63 (4.00, 5.10)		2.52 (1.40, 4.64)
eGFR*, ml/min			<.001	
Median (IQR)	100 (88, 111)	106 (96, 117)		104 (93, 115)
<60 , n(%)	5 (1.3%)	5 (0.8%)		10 (1.0%)
Total cholesterol, mg/dl			<.001	
Median (IQR)	184 (155, 209)	162 (139, 185)		170 (145, 197)
HDL cholesterol, mg/dl			<.001	
Median (IQR)	45 (37, 54)	39 (32, 47)		41 (34, 51)
LDL cholesterol, mg/dl			0.001	
Median (IQR)	109 (89, 131)	100 (82, 122)		104 (85, 126)
Tryglicerides, mg/dl			0.006	
Median (IQR)	111 (76, 170)	100 (75, 136)		104 (75, 151)
ALT, UI/mL			0.383	
Median (IQR)	27 (18, 40)	26 (18, 39)		26 (18, 39)

*CKD-Epi formula

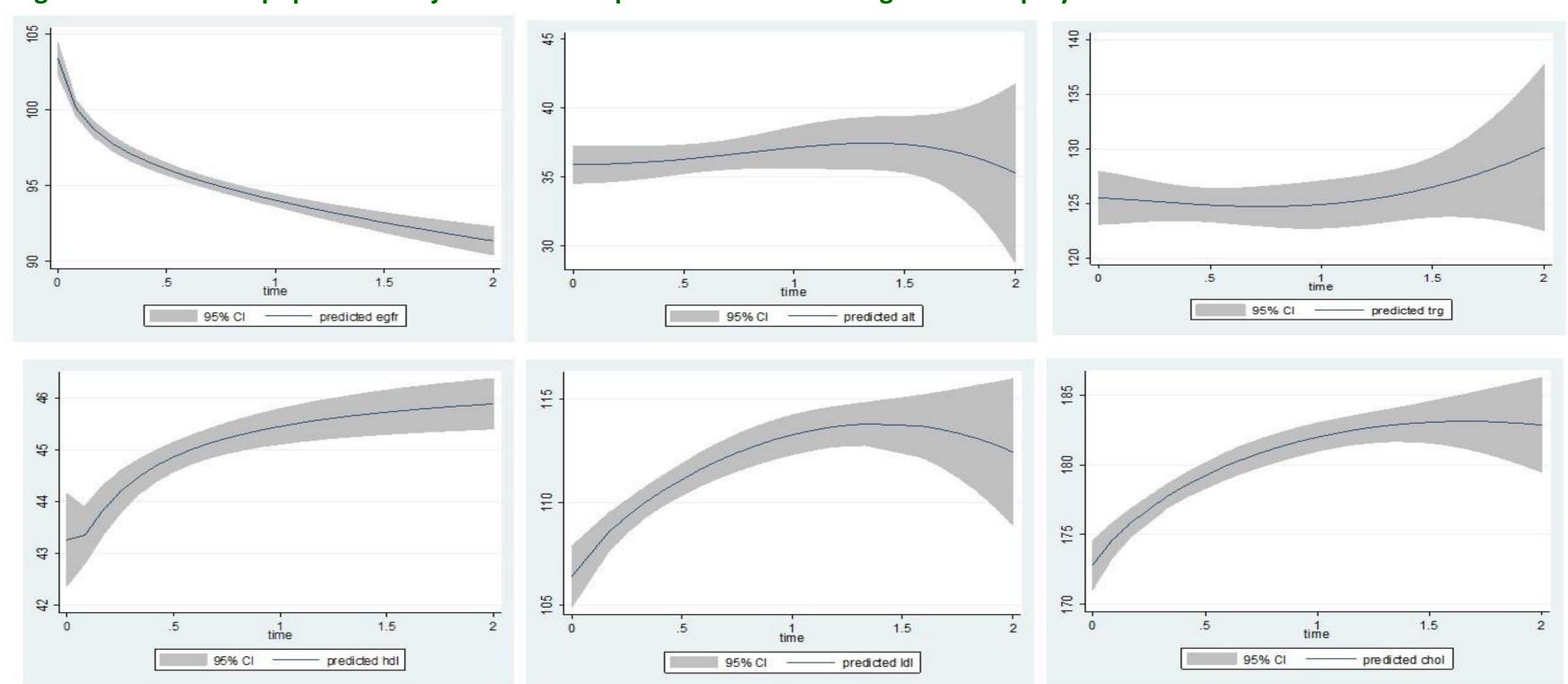## Figure 1 – Estimated population trajectories of lab parameters from fitting fractional polynomials

Table 2 – Mean values at baseline and slope/year stratified for selected baseline factors from fitting a mixed linear model

A)

	eGFR*		ALT		Triglycerides	
	Difference in baseline	Adjusted difference in change/year	Difference in baseline	Adjusted difference in change/year	Difference in baseline	Adjusted difference in change/year
Drug history						
ART-treated (Ref)						
ART-naïve	5.0 (2.8, 7.2)	-3.6 (-5.7, -1.5)	-2.5 (-7.8, 2.8)	-13.8 (-34.8, 7.2)	-10.7 (-19.6, -1.9)	12.1 (2.2, 22.0)
	<.001	<.001	0.359	0.198	0.017	0.017
Gender						
Male (Ref)						
Female	0.1 (-2.6, 2.8)	1.3 (-1.4, 4.0)	-13.0 (-19.4, -6.5)	-2.9 (-29.0, 23.3)	-4.6 (-15.5, 6.4)	-10.8 (-23.5, 1.9)
	0.952	0.336	<.001	0.830	0.414	0.094
Age, years						
0-60 (Ref)						
61+	-21.1 (-26.5, -15.7)	1.8 (-3.4, 7.0)	-0.5 (-13.9, 12.9)	-15.3 (-67.6, 37.1)	26.0 (3.7, 48.2)	8.5 (-15.7, 32.8)
	<.001	0.494	0.942	0.568	0.022	0.490
Calendar year						
2010-2015 (Ref)						
2016-2017	4.1 (1.9, 6.4)	-8.8 (-11.8, -5.9)	-5.5 (-11.0, -0.0)	-11.6 (-37.1, 14.0)	1.7 (-7.4, 10.8)	15.4 (0.4, 30.3)
	<.001	<.001	0.049	0.375	0.717	0.044
CD4 count, cells/mm3						
201+ (Ref)						
0-200	1.8 (-1.2, 4.8)	2.4 (-0.9, 5.7)	-0.8 (-8.2, 6.6)	8.9 (-23.9, 41.7)	22.5 (10.0, 34.9)	-14.5 (-30.1, 1.2)
	0.242	0.149	0.830	0.594	<.001	0.070
HIV-RNA, copies/mL						
0-100,000 (Ref)						
>100,000	3.5 (-0.1, 7.0)	-2.0 (-4.9, 0.9)	7.6 (-1.1, 16.4)	-5.9 (-34.8, 23.0)	14.1 (-0.6, 28.9)	7.1 (-6.7, 20.9)
	0.054	0.166	0.085	0.690	0.061	0.315

* by CKD-Epi formula

B)

	HDL-c		LDL-c		Total cholesterol (T-c)	
	Difference in baseline	Adjusted difference in change/year	Difference in baseline	Adjusted difference in change/year	Difference in baseline	Adjusted difference in change/year
Drug history						
ART-treated (Ref)						
ART-naïve	-4.8 (-6.7, -2.9)	2.7 (1.1, 4.3)	-7.6 (-11.9, -3.3)	4.4 (-0.2, 9.0)	-18.5 (-23.4, -13.6)	11.4 (6.1, 16.6)
	<.001	<.001	<.001	0.061	<.001	<.001
Gender						
Male (Ref)						
Female	10.4 (8.1, 12.6)	2.3 (0.4, 4.3)	0.0 (-5.4, 5.4)	0.4 (-5.4, 6.3)	13.3 (7.2, 19.4)	0.1 (-6.7, 6.9)
	<.001	0.021	0.998	0.886	<.001	0.985
Age, years						
0-60 (Ref)						
61+	-0.7 (-5.4, 4.0)	1.8 (-2.1, 5.6)	9.8 (-1.6, 21.3)	1.5 (-10.7, 13.7)	13.4 (0.8, 26.0)	4.4 (-8.8, 17.5)
	0.779	0.365	0.092	0.810	0.037	0.516
Calendar year						
2010-2015 (Ref)						
2016-2017	3.3 (1.3, 5.2)	-2.0 (-4.3, 0.3)	-3.2 (-7.7, 1.4)	-0.7 (-7.3, 5.9)	-0.1 (-5.2, 5.0)	2.9 (-4.6, 10.5)
	<.001	0.082	0.169	0.830	0.964	0.444
CD4 count, cells/mm3						
201+ (Ref)						
0-200	-3.4 (-6.1, -0.7)	5.0 (2.5, 7.5)	-10.5 (-16.6, -4.3)	11.3 (3.9, 18.7)	-7.7 (-14.5, -0.8)	8.5 (0.2, 16.9)
	0.013	<.001	<.001	0.003	0.028	0.046
HIV-RNA, copies/mL						
0-100,000 (Ref)						
>100,000	-5.7 (-9.1, -2.4)	2.9 (0.7, 5.1)	-10.9 (-18.3, -3.6)	6.1 (-0.5, 12.7)	-15.0 (-23.1, -6.8)	12.5 (5.1, 19.9)
	<.001	0.011	0.004	0.071	<.001	<.001

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