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# Clinical experience of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in real life practice: Data from the Turkish HIV-TR Cohort

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## Objective

Integrase inhibitors are now preferred drugs for initial antiretroviral treatment (ART). Tenofovir alafenamide (TAF), a pro-drug of tenofovir disoproxil fumarate (TDF) is associated with less renal and bone toxicity compared to TDF. Integrase inhibitors in single tablet pill forms are also effective switch options. Since its availability in October 2017, elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide (E/C/F/TAF) has been widely used in Turkey. We aimed to describe the effectiveness and tolerability of E/C/F/TAF in a real-life setting.

## Materials & Methods

We performed an observational, retrospective, multicentre cohort study with treatment-naive (TN) and treatment-experienced (TE) HIV patients starting E/C/F/TAF.

A standardized module in the web-based database was used to collect information.

Clinical, immuno-virological variables, switch reasons and changes in lipids and glomerular filtration rate (eGFR calculated using the CKD Epidemiology Collaboration (CKD-EPI) formula) were analysed at month-6 (M6) and -12 (M12).

Virologic outcomes were assessed in individuals with at least 6 months follow-up by a modified intention-to-treat approach (death or discontinuation of E/C/F/TAF=failure, missing data and lost to follow-up=excluded).

T-test for paired samples was used to analyse eGFR changes.

## Results

Baseline characteristics of 1743 persons (34% TN) from 32 HIV clinics are shown in Table 1.

Regimens received before switch to E/C/F/TAF were displayed in Table 2. Of the 1146 TE patients, 994 (86.7%) were virologically suppressed before switch [viral load (VL) <50 copies/mL].

Table-1. Baseline characteristics of the study population

| | Overall n (%) | Treatment Naive n (%) | Treatment Experienced n (%) |
|---|---|---|---|
| n (%) | 1743 (100) | 597 (100) | 1146 (100) |
| Male, n (%) | 1525 (87.5) | 536 (89.8) | 989 (86.3) |
| Age, years, median (IQR) | 35 (28-44) | 33 (27-43) | 35(29-45) |
| Pre-treatment CD4 cells/µL, median (IQR) | 568 (369-784) | 401.5 (263.5-554) | 673 (486-870) |
| Pre-treatment HIVRNA>100,000 copies/mL, n(%) | 278 (15.9) | 253 (42.4) | 25 (2.2) |
| Pre-treatment CD4 count <350 cells/µL, n(%) | 378 (21.7) | 245 (41.0) | 133 (11.6) |
| Transmission Mode | | | |
| Heterosexual | 837 (48.0) | 287 (48.1) | 550 (48.0) |
| MSM/Bisexual | 617 (35.4) | 204 (34.2) | 413 (36.0) |
| IDU | 4 (0.2) | 4 (0.7) | - |
| Unknown/Other | 285 (16.4) | 102 (17.1) | 183 (16.0) |

IQR: interquartile range, MSM: men who have sex with men, IDU: injection drug user

Table 2. ART regimens before E/C/F/TAF switch

| | n | % |
|---|---|---|
| **EVG/c/TDF/FTC** | 723 | 63.1 |
| **EFV/TDF/FTC** | 106 | 9.2 |
| **LPV/r/TDF/FTC** | 105 | 9.2 |
| **DTG/TDF/FTC** | 99 | 8.6 |
| **DRV/r/TDF/FTC** | 44 | 3.8 |
| **RAL/TDF/FTC** | 34 | 3.0 |
| **DTG/ABC/3TC** | 15 | 1.3 |
| **DTG/ZDV/3TC** | 7 | .6 |
| **EFV/ZDV/3TC** | 3 | .3 |
| **LPV/r/ZDV/3TC** | 3 | .3 |
| **LPV/r/RAL** | 2 | .2 |
| **NVP/TDF/FTC** | 2 | .2 |
| **NVP/ZDV/3TC** | 1 | .1 |
| **RAL/ZDV/3TC** | 1 | .1 |
| **LPV/r/EFV** | 1 | .1 |
| **Total** | 1146 | 100.0 |

**Abbreviations:** EVG/c: Elvitegravir/cobicistat, TDF: tenofovir disoproxil fumarate, FTC: emtricitabine, EFV: Efavirenz, LPV: Lopinavir, r: ritonavir, DTG: Dolutegravir, DRV: Darunavir, RAL: Raltegravir, ABC: Abacavir, 3TC: Lamivudine, ZDV: Zidovudine, NVP: Nevirapine

Main reasons for E/C/F/TAF switch were to prevent future toxicities (46.9%), intolerance/toxicity (17.3%) and treatment simplification (15.4%). Reasons for switching previous ART to E/C/F/TAF were displayed in Table 3.

Table 3. Reasons for switch to E/C/F/TAF

| | n | % |
|---|---|---|
| To prevent future toxicities | 538 | 46.9 |
| Intolerance/toxicity | 198 | 17.3 |
| Treatment simplification | 176 | 15.4 |
| Unknown | 79 | 6,9 |
| Provider's preference | 65 | 5.7 |
| Patient's willingness | 33 | 2.9 |
| Poor compliance | 17 | 1.5 |
| Virological failure | 9 | .8 |
| Drug-drug interaction | 3 | .3 |
| Low plasma concentration | 1 | .1 |
| Pregnancy related issues | 1 | .1 |
| Others | 26 | 2.3 |
| Total | 1146 | 100.0 |

Virologic and immunologic outcomes of treatment-naive and treatment-experienced patients are displayed in Table 4. At M12, 92.4% (315/341) of TN and 94.8% (674/711) of TE patients had a VL <50 copies/mL (Table 4). One adverse drug reaction leading to discontinuation (bruising), 1 SAE (myocardial infarction) and 4 deaths (3 TN and 1 TE patients) not related to E/C/F/TAF were documented during the study period. The patient who has experienced a new myocardial infarction one month after switching previous ART to E/C/F/TAF had a history of several coronary events. This patient had virological failure after 19 weeks during the course of the illness. At M12, median CD4 lymphocyte count increased by 229 and 38 cells/mm$^3$ in TN and TE patients, respectively.

Table 4. Outcome of treatment-naive and treatment–experienced patients

| | Treatment- naive n(%) (6 months) | Treatment- naive n(%) (12 months) | Treatment-experienced n(%) (6 months) | Treatment-experienced n(%) (12 months) |
|---|---|---|---|---|
| n(%) | 597 (100) | 407 (100) | 1146 (100) | 876 (100) |
| Lost to follow up, n(%) | 29 (4.9) | 40 (9.8) | 44 (3.8) | 97 (11.1) |
| Missing data, n(%) | - | 28 (6.4) | 16 (1.4) | 68 (7.8) |
| Treatment discontinuation, n(%) | 2 (0.4) | 6 (1.8) | 5 (0.5) | 11 (1.5) |
| Death, n(%) | 2 (0.4) | 3 (0.9) | - | 1 (0.1) |
| Evaluable patient, n(%) | 568 (95.1) | 341 (83.8) | 1086 (94.8) | 711 (81.2) |
| HIV RNA<50 copies/mL, n(%) | 491 (86.4) | 315 (92.4) | 1016 (93.5) | 674 (94.8) |
| Mean increases (±SD) in CD4 cell counts (cells/mL) | 175.9 (± 55.4) | 246.1 (± 40.6) | 50.2 (± 63.4) | 59.2 (± 20.7) |

Of 341 TN patients, 6 discontinued E/C/F/TAF in 12 months. Reasons for discontinuation were virologic failure (2), patients preference (1), drug-drug interaction (1), incompliance (1) and other (1). Antiviral resistance was newly detected in week 26 in a patient with virologic failure. Detected NRTI resistance mutations included K65N and K70R, and elvitegravir mutations E138K and Q148R in this patient. Virologic suppression was achieved with lopinavir/r and efavirenz. The other patient had a VL 230 copies/mL after 48 weeks of treatment and the regimen was switched to TDF/TFC/Dolutegravir. Virologic suppression was achieved after 5 months. This patient was back switched to E/C/F/TAF because of ALT increase > 5X ULN attributed to dolutegravir and maintained viral suppression.

In TE patients who switched from TDF to TAF, fasting lipid values increased compared to baseline while total/high density lipoprotein (HDL) cholesterol ratio did not change significantly. Median total cholesterol (TC), triglyceride, low density lipoprotein cholesterol, HDL cholesterol, non-HDL cholesterol and TC/HDL ratio increases at M12 were 19.5, 34, 9, 5, 13.5 mg/dL, and 0 respectively.

We observed an increase in mean (±SD) eGFR from baseline to M6 0.8±(0.9) ml/min/1.73 m$^2$ among 1002 patients switching from TDF to TAF (p<0.03). Changes in eGFR at M6 and M12 were more prominent among patients with baseline eGFR < 60 and 60-89 than ≥ 90mL/min/1.73m$^2$ (mean eGFR changes, 9.0±6.8 and 11.9±8.6; 6.0±6.4 and 5.8±6.3 vs -1.5 ± 5.1 and -1.7 ± 2.7, respectively, p=0.003). There were no differences in mean changes of eGFR between boosted and unboosted TDF containing regimens.

## Conclusions

E/C/F/TAF had a high virological efficacy in both TN and TE patients and was tolerated very well.

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