P2/15

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24-month evaluation of the German TAFNES cohort - Effectiveness, persistence and safety of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF), F/TAF + 3rd agent or rilpivirine/F/TAF (R/F/TAF) in treatment-experienced HIV-1 infected patients

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Background

Minimizing side effects and optimizing long-term tolerability of ART together with sustained viral suppression over time are essential requirements for achieving healthy ageing in people living with HIV (PLHIV). The prospective TAFNES cohort was initiated to provide evidence concerning effectiveness and safety of F/TAF-based regimens in routine clinical care.

Methods

Inclusion criteria for month 24 (M24) evaluation

- Treatment-experienced (TE) adults initiated on E/C/F/TAF, R/F/TAF or F/TAF + another 3rd agent according to the specific SmPCs (summaries of product characteristics). Additional inclusion criterion for the F/TAF+3rd agent group was age ≥50 years.
- Treatment start at least 21 months prior to data-cut (03/31/2019) and with either a documented visit within the predefined M24 visit window (between 21 and 27 months after F/TAF initiation) or a documented premature study/treatment discontinuation

Outcomes of interest

- ART persistence (Kaplan-Meier estimates; withdrawal of consent/loss to follow-up censored)
- Virologic effectiveness (HIV-RNA<50 cp/mL; discontinuation=failure, loss to follow-up/ withdrawal of consent/missing=excluded).
- Incident serious/non-serious adverse drug reactions (SADRs/ADRs)

Results

Study population

- N=434 TE patients were eligible for analysis; of which 151 were switched to E/C/F/TAF, 146 to F/TAF+3rd agent (32% dolutegravir, 17% nevirapine, 12% darunavir/ ritonavir, 11% raltegravir) and 137 to R/F/TAF; 93% of patients were switched from TDF-based ART.
- Reasons for switch (multiple responses allowed) to F/TAF-based ART were simplification (n=128, 29%), patient wish (n=130, 30%), side effects on previous ART (n=188, 43%), and other (n=77, 18%; including aiming to minimize long-term toxicity (n=56, 13%)).

Table 1. Baseline characteristics*

		Overall	E/C/F/TAF**	F/TAF + 3rd agent**	R/F/TAF**
N (%)		434 (100)	151 (35)	146 (34)	137 (32)
Male gender, n (%)		394 (91)	134 (89)	138 (95)	122 (89)
Age, years, median (IQR)		51 (40-58)	45 (36-54)	56 (53-61)	45 (35-52)
Age ≥50 years, n (%)		253 (58)	59 (39)	146 (100)**	48 (35)
CD4 count, cells/µL, median (IQR)		624 (467-830)	641 (493-888)	568 (423-780)	660 (500-809)
CDC stage C (AIDS), n (%)		91 (21)	34 (23)	35 (24)	22 (16)
HIV-RNA level (cp/mL)	<50, n (%)	403 (95)	137 (93)	139 (97)	127 (95)
	50 - <200, n (%)	14 (3)	7 (5)	3 (2)	4 (3)
	200 - 100,000, n (%)	7 (2)	3 (2)	2 (1)	2 (2)
	>100,000, n (%)	1 (<1)	1 (1)	0 (0)	0 (0)**
Previous antiretroviral regimen, n (%)					
	INI-based	158 (36)	97 (64)	55 (38)	6 (4)
	NNRTI-based	169 (39)	25 (17)	29 (20)	115 (84)
	PI-based	83 (19)	25 (17)	45 (31)	13 (9)
	Other	24 (6)	4 (3)	17 (12)	3 (2)

IQR, interquartile range; *Calculations are based on observed data; ***groups not comparable, e.g. due to different inclusion criteria (age ≥50 years for the F/TAF+ 3rd agent group and criteria based on the specific SmPCs [summaries of product characteristics])*

Incident ADRs/SADRs to M24

By M24, 26 ADRs (in 5.3% of participants [n=23]) and 6 SADRs (in 1% of participants [n=3]) were documented (see Table 2).

Table 2.

	ADRs and SADRs – per patient	Disc.*
E/C/F/TAF	- Pathological fracture	No
	- Weight increased	No
	- Weight increased	Yes
	- Headache, vertigo and hyperhidrosis	Yes
	- Headache, nausea	No
	- Dermatological ADR	Yes
	- Virologic failure**	Yes
	- Palpitations, headache (SADR)	Yes
F/TAF + 3rd agent (ADRs related to F/TAF)	- Sleep disorder	Yes
	- Lipodystrophy acquired	No
	- Arthropathy	Yes
	- Neuropsychiatric ADR	Yes
	- Metabolic ADR	Yes
	- Gastrointestinal ADR	Yes
	- Oesophageal dysplasia, gastric dysplasia, oesophageal carcinoma stage 0 (SADR)	No
R/F/TAF	- Libido decreased	Yes
	- Erectile dysfunction	Yes
	- Depression	Yes
	- Depression	Yes
	- Nightmare	Yes
	- Abdominal pain upper	Yes
	- Weight increased	Yes
	- Weight increased	Yes
	- Insomnia	No
	- Disturbance in attention	Yes
	- Fatigue (SADR)***	Yes

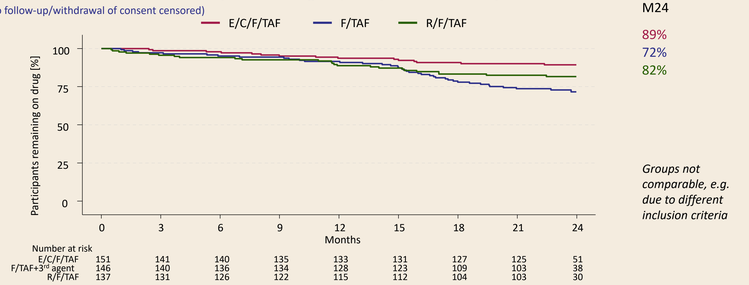
* Disc.: study drug discontinuation due to ADR
** documented as ADR, listed as virologic failure in Table 3
*** 'patient decision' was documented as the reason for discontinuation

Persistence on F/TAF-based regimens to M24

Estimated persistence on F/TAF-based ART was 81% at M24. The corresponding persistence in the subgroups using E/C/F/TAF, F/TAF+3rd agent or R/F/TAF was 89%, 72% and 82%, respectively (Figure 1).

Figure 1. Drug persistence to M24 by treatment group - Kaplan-Meier analyses

(loss to follow-up/withdrawal of consent censored)



Reasons for discontinuation to M24

In total, 25% of participants (n=109/434) discontinued by M24 visit. Reasons for discontinuation of E/C/F/TAF, F/TAF or R/F/TAF are shown in Table 3. Discontinuations in the F/TAF + 3rd agent group were driven by therapy simplification without virologic failure, i.e. switch from MTR to STR (multi to single tablet regimens).

Table 3. Reasons for study and/or study drug discontinuation, n (%)

	Overall	E/C/F/TAF	F/TAF + 3rd agent	R/F/TAF
Total discontinuations by M24; n/N (%)	109/434 (25)	27*/151 (18)	46*/146 (32)	36*/137 (26)
ADR	19** (4.4)	5** (3.3)	5 (3.4)	9 (6.6)
Therapy simplification	16 (3.7)	0 (0.0)	16 (11.0)	0 (0.0)
Patient decision	9 (2.1)	1 (0.7)	4 (2.7)	4 (2.9)
Drug-drug-interaction	6 (1.4)	5 (3.3)	0 (0.0)	1 (0.7)
Virologic failure (VF)	5 (1.2)	3 (2.0) [1]	0 (0.0)	2 (1.5) [2]
Investigator decision	5 (1.2)	0 (0.0)	5 (3.4)	0 (0.0)
Death	4 (0.9)	0 (0.0)	3 (2.1) [3]	1 (0.7) [4]
Withdrawal of consent	3 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
Other/unknown	16 (3.7)	1 (0.7)	7 (4.8)	8 (5.8)
Loss to follow-up	26 (6.0)	11 (7.3)	5 (3.4)	10 (7.3)

*including switches to (other) F/TAF-based single tablet regimens (see Table 5); **1x subjective intolerance, not documented as ADR;
[1]2 of 3 patients with HIV-RNA <50 cp/mL at baseline (BL), 1 pat. with missing value; 1 pat. without BL resistance test, but with multiple resistance associated mutations (RAMs) at VF incl. NNRTI mutations and thymidine analogue mutations (TAMs) indicative for historic VF (previous ART: DTG+F/TDF); 2 pts without resistance test at VF
[2]both patients with HIV-RNA <50 cp/mL at baseline; 1 pat. without RAMs at VF (previous ART R/F/TDF); 1 pat. without BL RAMs but RAMs at VF incl. TAMs (previous ART: DRV/r+F/TDF); [3]causes of death: 1x esophageal variceal bleeding, 1x sepsis, 1x thrombosis; [4]cause of death: 1x unknown

Virologic effectiveness

At M24 visit, 75% of patients included in the effectiveness analysis set had HIV-RNA levels <50 cp/mL, i.e. 84% of patients treated with E/C/F/TAF, 66% on F/TAF+3rd agent, and 76% on R/F/TAF (see Figure 2 and Table 4).

Figure 2. HIV-RNA <50 cp/mL

(discontinuation=failure, loss to follow-up/withdrawal of consent/missing=excluded)

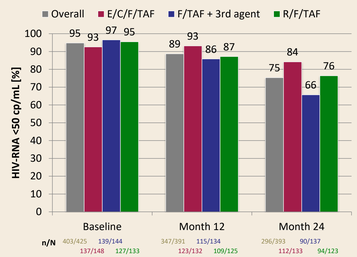


Table 4. Patient disposition and virologic outcomes at M24

	Overall	E/C/F/TAF	F/TAF + 3rd agent	R/F/TAF
Total, N	434	151	146	137
Loss to follow-up, n	26	11	5	10
Withdrawal of consent, n	3	1	1	1
Missing values, n	12	6	3	3
Effectiveness set, n (%)	393 (100)	133 (100)	137 (100)	123 (100)
HIV-RNA<50, n (%)	296 (75)	112 (84)	90 (66)	94 (76)
HIV-RNA<200, n (%)	13 (3)	4 (3)	5 (4)	4 (3)
HIV-RNA≥200, n (%)	4 (1)	2 (2)	2 (1)	0 (0)
Disc. due to VF, n (%)	5 (1)	3 (2)	0 (0)	2 (2)
Disc. for other reasons*, n (%)	75 (19)	12 (9)	40 (29)	23 (19)

*see table 3 for details; Disc.: study and/or study drug discontinuation; VF: virologic failure
Groups not comparable, e.g. due to different inclusion criteria

Post-study treatment regimens

The post-study treatment regimens are shown in Table 5. Of note, F/TAF remained as NRTI backbone in 42% of documented post-study regimens.

Table 5. Post-study regimens in F/TAF study drug discontinuers

		Overall	E/C/F/TAF	F/TAF + 3rd agent	R/F/TAF
Patients with documentation of post-study ART, n		77	16	38	23
Most common post-study regimens, n (%)	D/C/F/TAF	20 (26)	0 (0)	19 (50)	1 (4)
	R/F/TDF	7 (9)	1 (6)	0 (0)	6 (26)
	DTG/ABC/3TC	7 (9)	3 (19)	1 (3)	3 (13)
	E/C/F/TAF	6 (8)	N/A	4 (11)	2 (9)
	Other non-F/TAF-based ART	30 (39)	8 (50)	12 (32)	10 (43)
	Other F/TAF-based ART	6 (8)	3 (19)	2 (5)	1 (4)
	ART interruption	1 (1)	1 (6)	0 (0)	0 (0)

D: darunavir; C: cobicistat, TDF: tenofovir DF; DTG: dolutegravir; ABC: abacavir; 3TC: lamivudine; N/A: not applicable

Conclusions

- Overall persistence on F/TAF-based regimens was high in treatment-experienced PLHIV in Germany, >80% during 24 months of observation.
- Discontinuations and thereby effectiveness in the F/TAF+3rd agent group were driven by therapy simplification without virologic failure.
- Virologic effectiveness and safety were illustrated in a real world setting over 24 months with <5% discontinuations due to ADRs and <2% due to virologic failure.

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