P050

Effectiveness, persistence and safety of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF), rilpivirine/F/TAF (R/F/TAF) or F/TAF + another 3rd agent in HIV-1+ patients over 24 months – Results from the German TAFNES cohort study

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Background

The prospective TAFNES cohort study evaluates the effectiveness and safety of F/TAF-based single-tablet regimens (STRs) (with boosted elvitegravir or rilpivirine) or F/TAF-based multi-tablet regimens in people living with HIV (PLWH) in clinical routine in Germany.
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 PLWH. Here we present the data from the TAFNES cohort after 24 months of follow-up.

Methods

Inclusion criteria

- The analysis population consisted of treatment-naïve (TN) and treatment-experienced (TE) adult PLWH initiated on F/TAF-based single-tablet regimen with E/C/F/TAF or R/F/TAF or on F/TAF-based multi-tablet combinations with a 3rd agent (F/TAF+3rd agent) according to the specific SmPCs (summaries of product characteristics).
- In the TE F/TAF + 3rd agent group, only participants ≥ age 50 were included.

Month 24 (M24) outcomes

- Study/study drug persistence (Kaplan-Meier estimates; loss to follow-up is censored).
- Virologic effectiveness (HIV-RNA<50 cp/mL; discontinuation=failure, loss to follow-up and missing=excluded).
- Incident non-serious and serious adverse drug reactions (ADRs/SADRs) related to F/TAF or F/TAF-based STR coded with MedDRA Preferred Terms (PT).

Results

Study population

N=767 patients (TN: 301, TE: 466) were included in the analysis population: 318 patients received E/C/F/TAF, 192 R/F/TAF and 257 F/TAF+3rd agent (52% dolutegravir [DTG], 11% nevirapine [NVP], 10% darunavir/ritonavir [DRV/r], 9% raltegravir [RAL] and 18% other/or more than one 3rd agent). Among TN patients, 35% were late presenters (CD4 cell count <350/µl and/or AIDS), 19% with advanced disease (CD4 cell count <200/µl and/or AIDS). Late presentation was most common in the F/TAF+3rd agent group (49%). Of TE patients, 95% were on suppressive ART prior to switch. Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics

	Overall (N=767, 100%)	Treatment-naive (TN) patients (N=301, 100%)			Treatment-experienced (TE) patients (N=466, 100%)		
		E/C/F/TAF (n=159, 53%)	R/F/TAF (n=42, 14%)	F/TAF + 3rd agent (n=100, 33%)	E/C/F/TAF (n=159, 34%)	R/F/TAF (n=150, 32%)	F/TAF + 3rd agent[1] (n=157, 34%)
Male gender, n (%)	706 (92)	152 (96)	38 (90)	93 (93)	142 (89)	133 (89)	148 (94)
Age, years, median (IQR) [Range]	46 (34-54) [18-85]	36 (30-46) [19-72]	35 (30-43) [18-75]	40 (30-48) [18-74]	45 (36-54) [19-85]	45 (35-52) [23-79]	56 (53-61) [50-78]
CD4 count, cells/µL, median, (IQR)	556 (390-765)	498 (316-640)	483 (382-642)	353 (155-548)	632 (484-882)	667 (514-811)	568 (431-795)
HIV-1 RNA >100,000 cp/mL, n (%)	---	34 (22)	0 (0)	59 (60)	---	---	---
HIV-RNA <50 cp/mL, n (%)	---	---	---	---	145 (93)	136 (95)	149 (97)
CDC stage C, n (%)	126 (16)	10 (6)	1 (2)	17 (17)	37 (23)	22 (15)	39 (25)
Drug class of previous 3rd agent[2], n (%) INI:	---	---	---	---	102 (64)	6 (4)	57 (36)
Drug class of previous 3rd agent[2], n (%) NNRTI:	---	---	---	---	26 (16)	126 (84)	33 (21)
Drug class of previous 3rd agent[2], n (%) PI:	---	---	---	---	27 (17)	15 (10)	48 (31)
TDF-based previous antiretroviral regimen, n (%)	---	---	---	---	144 (91)	141 (94)	150 (96)

IQR, interquartile range; calculations are based on observed data; [1]inclusion criteria age ≥50y; [2]other ART combinations not presented;
Annotation: groups not comparable, e.g. due to different inclusion criteria

Study and/or study drug discontinuation

After two years >70% of patients on F/TAF-based ART were still under follow-up in the study. In total, 28% discontinued study medication and/or the study before M24. Reasons for discontinuation are shown in Table 2. Discontinuation in the F/TAF+3rd agent arm was driven by therapy simplification (switch from multi tablet to single tablet regimens). F/TAF remained as NRTI backbone in 54% of documented post-discontinuation regimens (Table 3).

Table 2. Reasons for discontinuation of study drug (E/C/F/TAF, R/F/TAF or F/TAF) and/or study

	Overall	E/C/F/TAF	R/F/TAF	F/TAF + 3rd agent
Total discontinuations by M24; n/N (%)	218/767 (28)	74/318 (23)	45/192 (23)	99/257 (39)
Therapy simplification	34 (4.4)	0 (0.0)	0 (0.0)	34 (13.2)
ADR	30 (3.9)	11 (3.5)	9 (4.7)	10 (3.9)
Patient decision	17 (2.2)	1 (0.3)	6 (3.1)	10 (3.9)
Investigator's discretion	14 (1.8)	4 (1.3)	1 (0.5)	9 (3.5)
Virologic failure (VF)[1]	12 (1.6)	6 (1.9)	4 (2.1)	2 (0.8)
Drug-drug-interaction	11 (1.4)	9 (2.8)	2 (1.0)	0 (0.0)
Withdrew consent	8 (1.0)	3 (0.9)	1 (0.5)	4 (1.6)
Death[2] (not related to study drug)	5 (0.7)	1 (0.3)	1 (0.5)	3 (1.2)
Other/unknown	16 (2.1)	3 (0.9)	5 (2.6)	8 (3.1)
Loss to follow-up	71 (9.3)	36 (11.3)	16 (8.3)	19 (7.4)

[1]3 of 12 patients with NRTI resistance mutations not related to F/TAF (indicating prior NRTI resistance); 2 without documented mutations at VF, and 7 without resistance follow-up; [2]sepsis, cardiac arrest, acute hemorrhagic shock caused by esophageal varices bleeding, thrombosis after surgical procedure of dysplasia esophageal and gastric, unknown

Table 3. Post-discontinuation regimens

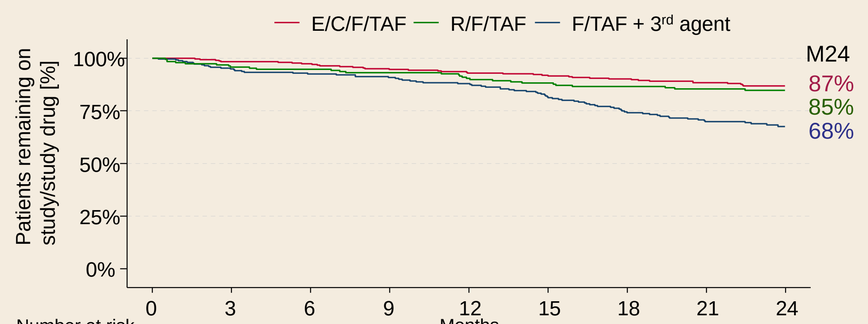
		Overall	E/C/F/TAF	R/F/TAF	F/TAF + 3rd agent
Patients[1] with documentation of post-discontinuation ART, n		129	33	25	71
Most common post-study regimens, n (%)	D/C/F/TAF	29 (22)	0 (0)	1 (4)	28 (39)
	DTG/ABC/3TC	15 (12)	7 (21)	4 (16)	4 (6)
	E/C/F/TAF	12 (9)	-	2 (8)	10 (14)
	DTG + F/TAF	12 (9)	10 (30)	2 (8)	0 (0)
	B/F/TAF	11 (9)	0 (0)	1 (4)	10 (14)
	R/F/TDF	9 (7)	2 (6)	6 (24)	1 (1)
	Other non-F/TAF-based ART	35 (27)	9 (27)	9 (36)	17 (24)
	Other F/TAF-based ART	6 (5)	5 (15)	0 (0)	1 (1)

D: Darunavir; C: Cobicistat, TDF: Tenofovir DF; DTG: Dolutegravir; ABC: Abacavir; 3TC: Lamivudine; B: Bictegravir
[1]Patients discontinuing study drug which was either E/C/F/TAF, R/F/TAF or F/TAF as part of cART

Persistence on study/study drug

Overall study/study drug persistence through M24 was 80% (TN: 78%, TE: 81%) (Figure 1).

Figure 1. Study/study drug persistence until month 24 by treatment group Kaplan-Meier analysis



Persistence estimated using Kaplan-Meier analysis censoring loss to follow-up; event=discontinuation of the study and/or F/TAF-based study medication (E/C/F/TAF, R/F/TAF or F/TAF); annotation: groups not comparable, e.g. due to different inclusion criteria

Virologic effectiveness at month 24

Overall virologic effectiveness was 74% (479/648) (E/C/F/TAF 83% [219/264], R/F/TAF 79% [127/160] and F/TAF+3rd agent 59% [133/224]) (Figure 2 and Table 4).

Figure 2. HIV-RNA <50 cp/mL
(discontinuation=failure, loss to follow-up/missing=excluded)

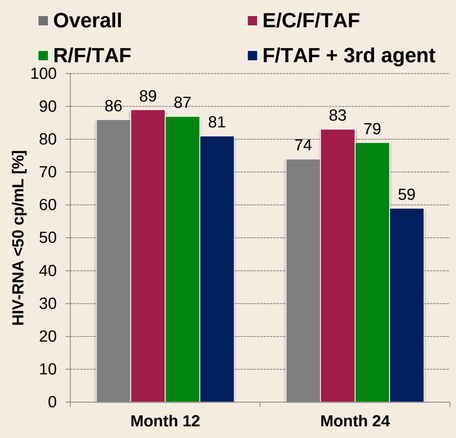


Table 4. Patient disposition and virologic outcomes at M24

	Overall	E/C/F/TAF	R/F/TAF	F/TAF + 3rd agent
Total, N	767	318	192	257
Loss to follow-up, n	71	36	16	19
Missing values, n	48	18	16	14
Effectiveness set, n (%)	648 (100)	264 (100)	160 (100)	224 (100)
HIV-RNA<50, n (%)	479 (74)	219 (83)	127 (79)	133 (59)
HIV-RNA<200, n (%)	17 (3)	5 (2)	4 (3)	8 (4)
HIV-RNA≥200, n (%)	5 (1)	2 (1)	0 (0)	3 (1)
Disc.* due to VF, n (%)	12 (2)	6 (2)	4 (3)	2 (1)
Disc.* for other reasons, n (%)	135 (21)	32 (12)	25 (16)	78 (35)

*Disc.: study and/or study drug discontinuation (see Table 2); VF: virologic failure;

Annotations: groups not comparable, e.g. due to different inclusion criteria; HIV-RNA measurements were assigned to the respective month using the laboratory date.

Safety

By M24, in 30 patients (3.9%), ADRs were the documented reason for study and/or study drug discontinuation, including 2 patients with virologic failure as documented ADR and 7 patients without further specification or documented ADR (Tables 3 and 5). Overall, 55 ADRs were reported including 3 serious adverse drug reactions (SADRs) in 6.1% of patients (n=43) (Table 5).

Table 5. Adverse drug reactions (ADRs) reported in the study

Subgroup	ADRs per patient	Pre.[1]	Disc.[2]	ADRs per patient	Pre.[1]	Disc.[2]
E/C/F/TAF	Blood HIV RNA increased[3]	TE	Yes	Headache, nausea	TE	No/No
	Dermatological ADR[4]	TE	Yes	Headache (SADR), palpitations (SADR)	TE	Yes/Yes
	Diarrhoea	TN	Yes	Headache, vertigo, hyperhidrosis	TE	Yes/Yes/Yes
	Diarrhoea, acne	TN	No/No	Loss of libido	TN	No
	Disturbance in attention, dizziness	TN	Yes/Yes	Migraine, sleep disorder	TN	Yes/Yes
	Dyspepsia, malaise, pruritus	TN	No/No/Yes	Nausea	TN	No
	Erectile dysfunction	TN	Yes	Pain in extremity	TE	Yes
	Fatigue	TN	No	Pathological fracture	TE	No
	Flatulence	TN	No	Pruritus	TN	No
	Headache	TN	No	Weight increased	TE	Yes
	Headache[4]	TN	Yes	Virologic failure[3]	TE	Yes
R/F/TAF	Abdominal pain upper	TE	Yes	Libido decreased	TE	Yes
	Depression	TE	Yes	Insomnia	TE	No
	Depression	TE	Yes	Nightmare	TE	Yes
	Erectile dysfunction[4]	TE	Yes	Weight increased	TE	Yes
	Fatigue	TE	Yes	Weight increased	TE	Yes
F/TAF + 3rd agent	Arthralgia	TE	Yes	Flatulence, vertigo, abnormal dreams	TN	No/No/No
	Constipation	TE	Yes	Headache[4], general feeling of illness[4]	TN	Yes/Yes
	Diarrhoea	TN	Yes	Nephropathy toxic	TN	Yes
	Diarrhoea	TE	Yes	Neuropsychiatric ADR[4]	TE	Yes
	Feeling unwell[4]	TN	Yes	Sleep disorder (SADR)	TE	Yes
	Feeling unwell[4]	TN	Yes			

[1]Pre.: Pretreatment; [2]Disc.: study drug (E/C/F/TAF, R/F/TAF or F/TAF) or study discontinuation due to serious (S)ADR; [3]Virologic failure documented as ADR [4]Not documented as ADR, but as F/TAF study drug discontinuation reason

Conclusions

The non-interventional TAFNES cohort analyzed clinical routine use of F/TAF-based HIV-1 therapies in n=767 PLWH in Germany. The final data cut after 24 months of follow up demonstrates:

- High persistence of F/TAF-based ART: 87% E/C/F/TAF, 85% R/F/TAF, 68% F/TAF+3rd agent
- Prolonged virologic effectiveness: 83% E/C/F/TAF, 79% R/F/TAF, 59% F/TAF+3rd agent
  – with only 1.6% of discontinuations due to virologic failure. Study drug discontinuation due to therapy simplification was common in the F/TAF+3rd agent arm, impacting the effectiveness result for this group.
- Low number of discontinuations due to ADRs: 3.9% of patients. Overall discontinuations were dominated by loss-to-follow up and simplification in this cohort.

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