

ORIGINAL ARTICLE

Effectiveness, safety, and patient-reported outcomes of emtricitabine/tenofovir alafenamide-based regimens for the treatment of HIV-1 infection: Final 24-month results from the prospective German TAFNES cohort study

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Abstract

Background: Tenofovir alafenamide (TAF) was introduced in the European Union in 2015 as a novel prodrug of tenofovir showing similar efficacy in clinical trials and a more favorable safety profile than tenofovir disoproxil fumarate (TDF). The German TAFNES cohort study (2016–2019) was conducted to generate real-world evidence.

Methods: Treatment-naïve (TN) and treatment-experienced (TE) people with HIV (PWH) receiving elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF), rilpivirine/F/TAF (R/F/TAF) or F/TAF + 3rd agent were included. Month (M) 24 outcomes included virologic effectiveness (HIV RNA <50 copies/mL), treatment persistence, adverse drug reactions (ADRs) and patient-reported outcomes, using the HIV Symptom Index (HIV-SI), 36-Item Short Form Health Survey (SF-36) and HIV Treatment Satisfaction (HIVTSQ) questionnaires.

Results: The study included 767 PWH (92% men, median age 46 years; 301 TN, 466 TE; E/C/F/TAF [$n = 318$], R/F/TAF [$n = 192$], F/TAF + 3rd agent [$n = 257$]). Among TN, 35% had late HIV diagnosis (CD4 < 350/ μ L and/or AIDS). Of TE, 95% were on suppressive antiretroviral therapy (ART) before switching. D:A:D (Data Collection on Adverse Effects of Anti-HIV Drugs) 5-year risks for chronic kidney disease were high for about 1 in 10 TN and 4 in 10 TE. Overall treatment persistence at M24 was 81% (E/C/F/TAF: 88%; R/F/TAF: 86%; F/TAF + 3rd agent: 70%, with ART simplification of multiple-tablet regimens in 13%). M24 viral

Hans-Jürgen Stellbrink is retired; his former affiliation at the time the study was conducted is stated.

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Funding information

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suppression (missing = excluded) was 96% (479/501). Discontinuations due to virologic failure or ADRs were rare, 2% (12/767) and 4% (30/767), respectively. HIV-SI and SF-36 summary scores improved in TN; HIVTSQ change scores showed an improvement in treatment satisfaction in TE.

Conclusion: Real-world data confirmed a favorable safety profile and high virologic effectiveness with high treatment satisfaction on F/TAF-based ART.

KEYWORDS

antiretroviral therapy, elvitegravir, F/TAF, real-world evidence, rilpivirine

INTRODUCTION

Opportunities for highly active antiretroviral therapy (ART) for people with HIV (PWH) have shifted toward higher safety and acceptability of long-term treatments. The development of tenofovir alafenamide (TAF) was such an example. TAF is an oral prodrug of the nucleotide analog tenofovir (TFV) and showed non-inferiority to the standard-of-care tenofovir disoproxil fumarate (TDF) in pivotal studies when co-formulated with boosted elvitegravir, rilpivirine or darunavir [1–5]. In clinical trials, while maintaining high virologic effectiveness, TAF demonstrated less nephrotoxicity and improved parameters for bone mineral density, both areas of concern for longer-term TDF use [6–9]. In recent years, the assessment of patient-reported outcomes (PROs) has increasingly been incorporated into clinical trials and observational studies to address patient needs beyond viral suppression. PRO measures help capture the impact of HIV/AIDS on patients' daily lives, including physical, emotional and social aspects.

The German TAFNES study focused on real-world effectiveness and safety as well as PROs of using E/C/F/TAF (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide), authorized by the European Medicines Agency (EMA) in November 2015. In April and June 2016, the cohort was expanded to observe use of fixed-dose combination F/TAF plus a 3rd agent, only in participants aged ≥ 50 years, and use of the single-tablet regimen (STR) R/F/TAF (rilpivirine/emtricitabine/tenofovir alafenamide), respectively, following their market authorization.

Here, we present final 24-month results from TAFNES, focusing on effectiveness of F/TAF-based regimens under real-world conditions, tolerability and safety of F/TAF-based ART and PROs.

METHODS

Design and study population

TAFNES was a prospective, multicentric, non-interventional, post-authorization safety study (PASS) (protocol GS-DE-292-1912) conducted between 2016 and 2019 that included treatment-naïve (TN) and treatment-experienced (TE) PWH initiated on E/C/F/TAF, R/F/TAF or F/TAF + 3rd agent in routine clinical care. Treatment decisions had to be independent from the conduct of this observational study and the enrollment of study participants. Per label, R/F/TAF was restricted to participants with HIV-RNA levels $\leq 100\,000$ copies/mL. Enrollment of TE in the F/TAF + 3rd agent subgroup was restricted to PWH aged ≥ 50 years. All participants were followed for 24 months.

Approval of the competent ethics committee had been obtained prior to enrollment of study participants, and the competent authorities (Federal Institute for Drugs and Medical Devices, the National Association of Statutory Health Insurance Physicians, the National Association of Statutory Health Insurers, and Association of Private Health Insurers) had been notified of the conduct of the cohort. All participants gave written informed consent before enrollment.

Outcomes of interest

The primary Month (M) 24 outcome measures were virologic effectiveness (HIV RNA < 50 copies/mL) and CD4 cell count changes from baseline (prior to TAF-based ART) based on observed data. Virologic effectiveness was quantified using a missing = excluded (M = E) approach (excluding missing values/discontinuations from the effectiveness set); discontinuations are reflected in the analysis of treatment persistence.

Secondary variables and outcomes of interest included reasons for ART choice, persistence on 'study drugs' (defined as E/C/F/TAF, R/F/TAF or F/TAF as dual fixed dose combination), reasons for discontinuation, and development of drug resistance, as well as safety parameters such as serious and non-serious adverse drug reactions (SADRs/ADRs) (coded with Medical Dictionary for Regulatory Activities [MedDRA] preferred terms [10]) and renal function parameters, namely change from baseline in serum creatinine (sCr) and estimated glomerular filtration rate (eGFR) calculated with MDRD and Cockcroft–Gault equations as defined in the Statistical Analysis Plan of the TAFNES cohort [11, 12]. The validated short and full D:A:D (Data Collection on Adverse Effects of Anti-HIV Drugs) risk scores for chronic kidney disease (CKD; confirmed eGFR ≤ 60 mL/min/1.73 m²) in PWH were used to estimate the 5-year risk of developing CKD [13]. The CKD risks scores were calculated for baseline (i.e., prior to TAF-based ART) and changes from baseline were calculated for M24. For the short score, variables included were intravenous drug use (IVDU), hepatitis C, four age categories, three categories for baseline eGFR, sex and CD4 nadir $\leq 200/\mu\text{L}$; along with the variables of the short score, the variables hypertension, cardiovascular disease and diabetes mellitus were included for the full CKD score. Missing information (e.g., 'IVDU') was omitted from the score, 'hypertension' was equated with 'patient on treatment for hypertension' and 'CD4 nadir' was equated with current CD4 cell count. Subjects with a baseline eGFR ≤ 60 mL/min/1.73 m² were excluded. Scores <0 , 0–4 and ≥ 5 indicate low/medium/high CKD risk, respectively (associated with 5-year CKD risks of 1:393 [0.3%], 1:47 [$\approx 2.5\%$] and 1:6 [$\approx 14\%$] in the D:A:D cohort).

PROs were assessed at M24 and/or M12 using the HIV Symptom Index (HIV-SI) questionnaire, the 36-Item Short Form Health Survey (SF-36) and the HIV Treatment Satisfaction status and change questionnaires (HIVTSQs and HIVTSQc). With the 20-item HIV-SI, symptom distress is recorded (total score range, 0–80; higher score = greater distress [14]). The SF-36 measures health-related quality of life (HRQoL), resulting in physical and mental component scores (PCS and MCS) using norm-based scoring with a mean = 50 and SD = 10 (higher scores = greater HRQoL; with a score above 50 representing better than average and below 50 poorer than average function of a predefined normative population) [15, 16]. The 10-item HIVTSQs and HIVTSQc assess PWH-specific treatment satisfaction; total scores range from 0 to 60 and from –30 to +30, respectively (higher status scores indicate greater treatment satisfaction and positive change score indicates an improvement) [17].

Statistical methods and stratification variables

Descriptive statistics were used to summarize baseline characteristics and outcome variables. Analyses were based on available observed data, without imputation of variables. Quantitative variables were summarized using median and interquartile range (lower quartile [Q1], upper quartile [Q3]). Kaplan–Meier analyses were used to evaluate persistence (censoring loss to follow-up, withdrawal of consent, and death). Statistical tests were performed only for exploratory reasons (no hypothesis testing). The α -level for significance was set at <0.05 and was not adjusted for multiple testing. Analyses were performed using Stata v.15.1 (StataCorp LLC, College Station, Texas, USA).

All analyses were stratified by study group and separately for TN and TE. Further stratification followed by age (<50 , 50–64, ≥ 65 vs. <50 , ≥ 50 years), sex (male/female) and ethnicity. Results are only shown for $p < 0.05$ between-group differences. In addition, for persistence, effectiveness and PROs, TN were stratified by presence of late diagnosis (LD; CD4 cell count $<350/\mu\text{L}$ and/or Centers for Disease Control and Prevention [CDC] [18] stage C [clinical AIDS] at baseline) and presence of LD with advanced disease (CD4 cell count $<200/\mu\text{L}$ and/or CDC stage C at baseline).

RESULTS

Study population

Recruitment took place between January 2016 and November 2017. The disposition of study participants is shown in Figure S1 (supplement). Overall, 767 participants were included in the final analysis set (FAS; $n = 301$ TN, $n = 466$ TE). In the F/TAF + 3rd agent group, the most common 3rd agents combined with F/TAF were dolutegravir (52%), nevirapine (11%), darunavir/ritonavir (11%) and raltegravir (9%). Baseline demographic and clinical characteristics are shown in Table 1.

Of 466 TE participants, 50% switched from an STR; 93% from TDF. The median (Q1, Q3) time on TDF before switching was 29.9 (17.1, 60.3) months, and 81% had taken TDF for ≥ 1 year. Altogether, 68% only replaced TDF with TAF ($n = 318$) (TDF/TAF switcher).

In the E/C/F/TAF group, 64% (102/159) had previously been on integrase strand transfer inhibitor (INSTI)-based ART. In the R/F/TAF group, 84% (126/150) had been on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART, and for 91% (143/157) of participants in the F/TAF+3rd agent-group, the 3rd agent remained in the same drug class (Table 1).

TABLE 1 Study participants' baseline demographic and clinical characteristics.

Characteristic	Overall (N = 767)	TN (n = 301)			TE (n = 466)		
		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 ^a (n = 157, 34%)
Male sex, antiretroviral (%)	706 (92)	152 (96)	38 (90)	93 (93)	142 (89)	133 (89)	148 (94)
Age, years, median (Q1, Q3) [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]
<50 years, n (%)	445 (58)	132 (83)	37 (88)	81 (81)	99 (62)	96 (64)	0 (0)
50–64 years, n (%)	274 (36)	24 (15)	4 (10)	18 (18)	48 (30)	47 (31)	133 (85)
≥65 years, n (%)	48 (6)	3 (2)	1 (2)	1 (1)	12 (8)	7 (5)	24 (15)
Race, n (%)							
White	709 (93)	143 (93)	38 (90)	91 (92)	148 (94)	136 (91)	153 (97)
Black	31 (4)	5 (3)	2 (5)	5 (5)	9 (6)	7 (5)	3 (2)
CD4 count, cells/μL, median (Q1, Q3)	556 (390, 765)	498 (316, 640)	483 (382, 642)	353 (155, 548)	632 (484, 882)	667 (514, 812)	568 (431, 795)
HIV-1 RNA >100 000 copies/mL, n (%)	–	34 (22)	0 (0)	59 (60)	–	–	–
HIV-1 RNA <50 copies/mL, n (%)	–	–	–	–	146 (93)	136 (95)	149 (97)
CDC stage C, n (%)	126 (16)	10 (6)	1 (2)	17 (17)	37 (23)	22 (15)	39 (25)
Late diagnosis, ^b n (%)	–	47 (30)	9 (22)	49 (49)	–	–	–
Advanced disease, ^c n (%)	–	23 (15)	2 (5)	31 (31)	–	–	–
Previous 3rd agent class, ^d n (%)							
INSTI	–	–	–	–	102 (64)	6 (4)	57 (36)
NNRTI	–	–	–	–	26 (16)	126 (84)	33 (21)
PI	–	–	–	–	27 (17)	15 (10)	48 (31)
Previous STR, n (%)	–	–	–	–	107 (67)	121 (81)	5 (3)
TDF-based previous antiretroviral regimens, n (%)	–	–	–	–	144 (91)	141 (94)	150 (96)
Solely switched from TDF to TAF					85 (53)	101 (67)	132 (84)

Note: Q1 and Q3, lower and upper quartile; calculations are based on observed data.

Abbreviations: CDC, Centers for Disease Control and Prevention; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; R/F/TAF, rilpivirine/F/TAF; STR, single-tablet regimen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TE, treatment-experienced; TN, treatment-naïve.

^aInclusion criteria age ≥50 years.

^bCD4 cell count <350/μL and/or AIDS.

^cCD4 cell count <200/μL and/or AIDS.

^dOther antiretroviral therapy combinations not presented; annotation: groups not comparable (e.g., due to different inclusion criteria).

The proportion of participants with ≥1 comorbidity was 50% (356/714; 37% E/C/F/TAF, 55% R/F/TAF, 63% F/TAF + 3rd agent) with a higher

prevalence in older participants (70% ≥50 vs. 36% <50 years). Comorbidities present in ≥5% of participants included hypertension (15%), neuropsychiatric

disorders (11%), hyperlipidemia (6%) and cardiovascular diseases (5%).

Reasons for F/TAF-based antiretroviral treatment

Most common reasons for F/TAF-based ART initiation in TN were early treatment initiation according to local and current guidelines (69%), patient preference (39%) and treatment as prevention (28%) (multiple responses possible) (Table S1). TE switched most frequently due to side effects of current ART (43%), patient preference (30%) and ART simplification (29%). For 13% of TE, wishing to avoid long-term toxicities (all on TDF-based ART) was prominent among 'other' reasons cited.

Treatment persistence, discontinuations, virologic and immunologic effectiveness

At M24, 72% (549/767) of participants were still on study drugs under follow-up in the study: 77% on E/C/F/TAF, 77% on R/F/TAF and 61% on F/TAF in the F/TAF + 3rd agent group. Five participants (0.7%) died for reasons unrelated to F/TAF (4 TN: acute hemorrhagic shock caused by oesophageal varix bleeding, sepsis, thrombosis after surgical procedure of oesophageal and gastric dysplasia, cardiac arrest; 1 TN: reason unknown) and 9% were lost to follow-up. Overall, 17% ($n = 133$) of the participants discontinued study drugs before M24 after a median (Q1, Q3) time of 13.1 (6.0, 17.3) months.

Reasons for study drug discontinuation are shown in Table 2. Overall study drug persistence through M24

(Kaplan–Meier estimate) was 81% (Figure 1). There were no differences between TN (80%) and TE (82%). Among TN participants, no differences in persistence were found between LD (76%; LD with advanced disease 74%) and non-LD (81%).

At M24, 96% (479/501) of participants reached HIV RNA <50 copies/mL (on-treatment analysis, M = E). Virologic outcomes in TN and TE by treatment groups are shown in Figure 2. In LD, 95% had an HIV-RNA level < 50 copies/mL at M24 (LD with advanced disease 90%).

Of note, there were 12 (2%) study drug discontinuations due to virologic failure (4 TN, 8 TE), including 3 with HIV RNA <50 copies/mL (0, 31 and 32 copies/mL) and 4 with HIV RNA >200 copies/mL before discontinuation (247, 274, 2400 and 49 000 copies/mL; Table 2).

In a subgroup analysis by sex, age and treatment status, significant differences were seen in treatment (F/TAF) persistence between males and females (82% vs. 70%; $p = 0.023$). Proportions of discontinuations differed between age groups <50 and ≥ 50 years (13% vs. 8%; $p = 0.014$) and treatment status (12% TN vs. 8% TE; $p = 0.001$). Discontinuation in the F/TAF + 3rd agent group was mainly attributed to simplification to STRs.

In TN participants, the median (Q1, Q3) absolute CD4 cell change was +292/ μ L (138, 450; $n = 182$). In LD, median CD4 change was 301/ μ L (180, 439; LD with advanced disease, 302 [210, 410]) versus 274/ μ L (78, 450) in non-LD. In TE, the median CD4 change was +52/ μ L (−81, 146; $n = 303$). With increasing age, median baseline CD4 cell counts were slightly lower, as were CD4 cell changes by M24 (data not shown).

TABLE 2 Reasons for study drug discontinuation.

Parameter	Overall	%	E/C/F/TAF	%	R/F/TAF	%	F/TAF + 3rd agent	%
Study drug ^a discontinuations by M24, n/N	133/767	17.3%	34/318	10.7%	27/192	14.1%	72/257	28.0%
Adverse drug reaction	30	3.9%	11	3.5%	9	4.7%	10	3.9%
Virologic failure ^b	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%
Therapy simplification	34	4.4%	0	0.0%	0	0.0%	34	13.2%
Patient decision	17	2.2%	1	0.3%	6	3.1%	10	3.9%
Investigator's discretion	13	1.7%	4	1.3%	1	0.5%	8	3.1%
Other/not specified	16	2.1%	3	0.9%	5	2.6%	8	3.1%

Abbreviations: E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; M, month; NRTI, nucleoside reverse transcriptase inhibitor; R/F/TAF, rilpivirine/F/TAF.

^aStudy drug is either E/C/F/TAF, R/F/TAF or F/TAF as dual fixed dose combination.

^b3/12 participants with resistance-associated mutations indicating prior NRTI resistance; 1 without documented mutations at virologic failure, and 8 without resistance follow-up; individual HIV RNA levels prior to/at discontinuation were 0, 31, 32, 97, 100, 100, 134, 158, 247, 274, 2400 and 49 000 copies/mL.

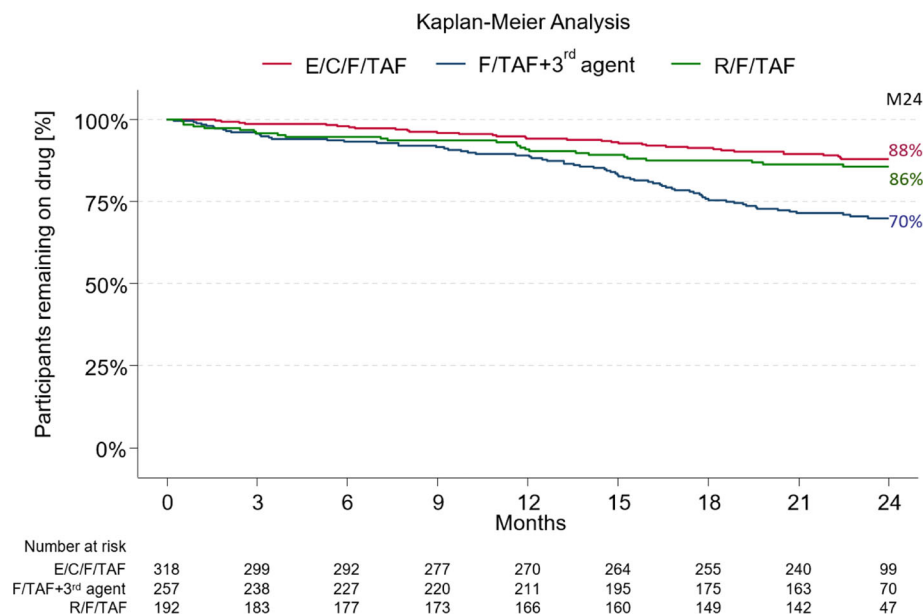


FIGURE 1 Persistence to study drugs (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF], rilpivirine/F/TAF [R/F/TAF] and F/TAF+3rd agent) by study group.

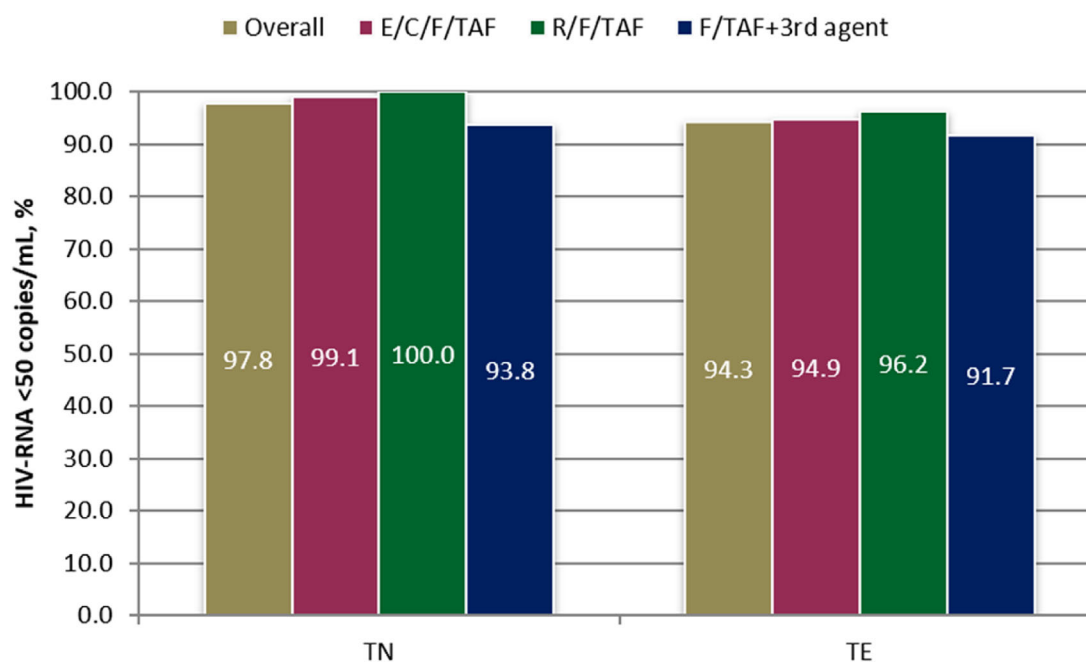


FIGURE 2 Virologic effectiveness at M24, by study group arm (missing = excluded approach, on-treatment analysis); effectiveness set, $n = 501$. E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; R/F/TAF, rilpivirine/F/TAF; TE, treatment-experienced; TN, treatment-naïve.

HIV drug resistance

Availability of genotypic resistance testing before initiation of F/TAF-based ART was documented in 356 participants (46% of cohort). In 178 participants (23% of cohort), resistance-associated mutations (RAMs) and polymorphisms were documented (Table S2,

supplement), with few participants harboring *M184V* or INSTI RAMs. Virologic outcomes in participants with known baseline RAMs and polymorphisms are depicted in Table S3 (supplement). Despite a high rate of baseline RAMs (NRTI 24%, NNRTI 27%, protease inhibitor [PI] 6%, INSTI 3%), overall suppression rate at last follow-up was 94%.

Resistance development during follow-up was tested in 16 participants (2% of cohort); RAMs/polymorphisms were documented in only 7 – all considered not, or only partially, associated with TAF-based ART (Table S4, supplement).

Follow-up antiretroviral regimens

For 129 of 133 participants having discontinued study drugs, follow-up ART was documented; of those, 54% stayed on a TAF-based regimen (69% [49/71] of the F/TAF + 3rd agent group; with 39% [28/71] switching to STR D/C/F/TAF). The most common follow-up regimens ($n \geq 5$) were D/C/F/TAF (22%), abacavir/lamivudine/dolutegravir (ABC/3TC/DTG; 12%), DTG + F/TAF (9%), E/C/F/TAF (9%), bicitegravir (B)/F/TAF (9%), rilpivirine (RPV)/FTC/TDF (7%) and DTG + 3TC (4%).

Safety

ADRs and SADR are listed in Table 3. Overall, 58 ADRs (related to F/TAF) were documented in 54 participants (7% of study population), of which 30 (4% of study population) discontinued F/TAF or the respective STR. Virologic failure was documented as ADR in 2 TE participants (with >200 HIV RNA copies/mL), leading to study drug discontinuation. Three participants experienced a SADR.

Of note, for participants with documented weight at baseline and M24 ($n = 383$), median (Q1, Q3) weight change was +3.0 kg for TN (0.0, +7.5, $p < 0.0001$; $n = 127$), +1.8 kg for TE (−1.0, +5.0, $p < 0.0001$; $n = 256$) and +1.6 kg for TE previously on TDF-based last ART (−1.0, +5.0, $p < 0.0001$; $n = 237$).

Renal parameters and CKD score

TN participants

In TN participants, at M24, there was a median increase in sCr of +0.1 mg/dL ($n = 178$; $p < 0.0001$) and a significant decrease in eGFR (MDRD) [mL/min/1.73 m²] (median −11.3 [Q1, Q3: −21.2, −1.6]; $n = 177$; $p < 0.001$), observed at M3 visit, which stabilized thereafter. Although still significant, the median change in eGFR was lower when using the Cockcroft–Gault formula (−3.2 mL/min [−17.4, 6.5]) in a smaller sample ($n = 119$; based on availability of covariables for the equation). The full CKD risk score was available for 253 TN at baseline; 2% of TN were excluded for the score

calculations due to a eGFR < 60 mL/min/1.73 m² at baseline. For TN, baseline CKD risk was categorized as low in 78%, medium in 14% and high in 8%; in these groups, the calculated median (Q1, Q3) 5-year risks for CKD were 0.20% (0.1, −0.4), 2.1% (1.1, 2.1) and 7.1% (5.4, 11.2), respectively. The overall median change 5-year CKD risk (full score) in TN was 0.0% (0, 0.6). Full and short scores showed similar results (data not shown).

TE participants

In TE participants, at M24, there were no significant changes for sCr, whether stratified by treatment or age group. Among TDF/TAF switchers ($n = 214$), a median change in sCr of −0.03 mg/dL was observed (Q1, Q3: −0.1, 0.1).

Overall, eGFR (MDRD) [mL/min/1.73 m²] was stable in TE. Among TDF/TAF switchers, there was a trend ($p < 0.1$) towards an increase in eGFR (MDRD) (+1.7 mL/min/1.73 m² [median]); in the group switching from non-TDF to TAF, there was a trend towards a decrease (−2.7 mL/min/1.73 m²). In TDF/TAF switchers, the increase in eGFR was more prominent for participants with baseline eGFR (MDRD) < 60 mL/min/1.73 m² (+5.7; $p = 0.003$). These results were also observed for eGFR (Cockcroft–Gault) [mL/min].

The full CKD risk score was calculated at baseline for 365 TE participants; 7% of TE were excluded from the score calculation due to an eGFR < 60 mL/min/1.73 m² at baseline. Risk was categorized as low for 36%, medium for 27% and high for 38%; median (Q1, Q3) 5-year risks were 0.4% (0.1, −0.4), 2.1% (1.4, 2.1) and 8.0% (5.4, 25.1), respectively. Overall, full and short risk scores showed similar results (data not shown). The 5-year CKD risk (full score) showed an increase within age groups with a median risk of 0.4% ($n = 166$), 5.4% ($n = 178$) and 20.1% ($n = 21$) for age groups <50, 50–64 and ≥ 65 years, respectively.

At M24, the overall median change in 5-year CKD risk was 0.0% (Q1, Q3: 0.0, 0.8; $n = 178$; $p < 0.001$; full score) indicating stable CKD risk in most participants. The median change in the 5-year CKD risk was estimated at 0.0% (0.0, 0.6; $n = 127$) among TDF/TAF switchers, in comparison with 0.0% (0.0, 1.7; $n = 51$) in all others.

Patient-reported outcomes

Symptom distress: HIV-SI questionnaire

For participants who completed questionnaires at baseline as well as M24 (TN: $n = 128$, 43%; TE: $n = 206$,

TABLE 3 Adverse drug reactions and serious adverse drug reactions of individual participants reported in the study, coded by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

Subgroup	ADRs per patient	TN/TE	Disc ^a	ADRs per patient	TN/TE	Disc ^a
E/C/F/TAF	Blood HIV RNA increased ^b	TE	Yes	Headache (SADR), palpitations (SADR)	TE	Yes/Yes
	Dermatological ADR ^c	TE	Yes	Headache, vertigo, hyperhidrosis	TE	Yes/Yes/Yes
	Diarrhea	TN	Yes	Loss of libido	TN	No
	Diarrhea, acne	TN	No/No	Migraine, sleep disorder	TN	Yes/Yes
	Disturbance in attention, dizziness	TN	Yes/Yes	Nausea	TN	No
	Dyspepsia, malaise, pruritus	TN	No/No/Yes	Pain in extremity	TE	Yes
	Erectile dysfunction	TN	Yes	Pathological fracture	TE	No
	Fatigue	TN	No	Pruritus	TN	No
	Flatulence	TN	No	Weight increased	TE	No
	Headache	TN	No	Weight increased	TE	Yes
	Headache ^c	TN	Yes	Virologic failure ³	TE	Yes
	Headache, nausea	TE	No/No			
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 ^c	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, general feeling of illness ⁴	TN	Yes/Yes
	Diarrhea	TN	Yes	Nephropathy toxic	TN	Yes
	Diarrhea	TE	Yes	Neuropsychiatric ADR ⁴	TE	Yes
	Feeling unwell ^c	TN	Yes	Oesophageal dysplasia, gastric dysplasia, oesophageal carcinoma (SADR)	TE	No/No/No
	Feeling unwell ^c	TN	Yes	Sleep disorder (SADR)	TE	Yes

Abbreviations: ADR, adverse drug reaction; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; PT, preferred term; R/F/TAF, rilpivirine/F/TAF; SADR, serious adverse drug reaction; TE, treatment-experienced; TN, treatment-naïve.

^aDisc: Study drug (E/C/F/TAF, R/F/TAF or F/TAF) or study discontinuation due to SADR.

^bVirologic failure documented as ADR (last HIV RNA-1 value before/at discontinuation: 247 copies/mL).

^cNot documented as ADR but documented as reason for study drug (F/TAF) discontinuation.

44%), baseline median (Q1, Q3) HIV-SI score was 10.0 (4.0, 19.0) for TN and 9.0 (3.0, 19.0) for TE; M24 median score was 6.5 (2.0, 13.0) for TN and 9.0 (3.0, 18.0) for TE.

A significant improvement was only seen in TN, with a median change of -2.0 (-10.0 , $+3.0$; $p < 0.001$) points. In LD ($n = 44$) and LD with advanced disease ($n = 20$), median changes from baseline were -3.0 (-11.0 , $+4.5$; $p = 0.016$) and -6.5 (-14.5 , $+4.5$; $p = 0.048$), respectively.

Health-related quality of life: SF-36 mental and physical components

Altogether, 45% of participants completed questionnaires at baseline and M24 (TN: $n = 129$, 43%; TE: $n = 216$, 46%). For the MCS and PCS scores, a significant improvement was seen in TN, including LDs and LD with advanced diseases (Table 4).

TABLE 4 36-Item Short Form Health Survey (SF-36): baseline and Month 24 outcomes, and changes from baseline.

Parameter	Treatment-naïve ^a (<i>n</i> = 129)	Late diagnosis ^a (<i>n</i> = 43)	Late diagnosis with advanced disease ^b (<i>n</i> = 19)	Treatment- experienced (<i>n</i> = 216)
Mental component, ^c median (Q1, Q3)				
Baseline	47.8 (38.0, 54.5)	42.4 (34.2, 54.3)	42.4 (34.2, 52.1)	51.6 (42.7, 56.3)
M24	53.2 (44.7, 56.9)	52.5 (45.8, 57.8)	48.7 (43.2, 56.9)	51.7 (41.4, 57.4)
Change from baseline	+3.5*** (−2.8, +10.9)	+6.3*** (−1.9, +16.8)	+6.3** (−2.0, +14.7)	+0.7 (−4.3, +5.7)
Physical component, ^c median (Q1, Q3)				
Baseline	57.0 (51.0, 60.3)	54.2 (46.2, 59.4)	47.6 (40.2, 56.2)	56.7 (46.6, 60.7)
M24	59.1 (54.4, 60.6)	59.1 (51.9, 60.5)	56.5 (51.6, 60.4)	56.9 (49.4, 60.5)
Change from baseline	+1.2* (−1.8, +4.6)	+1.7* (−1.2, 8.0)	+7.7** (+1.4, +16.4)	−0.4 (−4.4, +3.5)

Note: Participants completed questionnaires at baseline and M24.

****p* < 0.001, ***p* < 0.01, **p* < 0.05 (based on univariate testing; statistical tests were performed only for exploratory reasons (no hypothesis testing; no adjustment for multiple testing).

Abbreviations: HRQoL, higher health-related quality of life; M, month; MCS, mental component score; PCS, physical component score; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

^aCD4 cell count <350/μL and/or AIDS.

^bCD4 cell count <200/μL and/or AIDS.

^cNorm-based scoring for the SF-36 PCS and MCS with a mean of 50 and a SD of 10; higher scores indicate HRQoL [15].

HIVTSQs and HIVTSQc questionnaires (TE participants)

At baseline, the HIVTSQs questionnaire was completed by 84% (393/466) of TE participants, with a median (Q1, Q3) status score of 55 (50, 59). For TE completing both baseline status (HIVTSQs) and M12 change (HIVTSQc) questionnaires (51%), median (Q1, Q3) HIVTSQ change score at M12 was +15.5 (3, 27) (*p* < 0.01); median change scores across study groups were +21.0 (8, 29) for E/C/F/TAF (*n* = 87), +14.0 (0, 27) for R/F/TAF (*n* = 84) and +10.0 (1, 27) for F/TAF + 3rd agent (*n* = 67). Median M12 change scores (Q1, Q3) were +26.5 (19, 30) in females (*n* = 22), +15.0 (2, 27) in males (*n* = 216), +22.0 (11, 29) in participants changing to STR from a multiple-tablet regimen (*n* = 50) and +22.0 (3, 28) in older participants (≥65 years; *n* = 18).

DISCUSSION

TAFNES was one of the first prospective cohorts collecting real-world data on the use of F/TAF-based antiretroviral regimes in PWH, particularly E/C/F/TAF, R/F/TAF or F/TAF plus other 3rd agent. Compared with clinical trial populations [2, 5, 7, 20–22], the German TN participants were of similar age (36 years median) with fewer females (6%; in the TE group, 9%) and only 4% Black (in international studies, 19%–25%). In comparison, by

the end of 2017, about 20% of PWH in Germany were female [23]. In the F/TAF+ 3rd agent group, 60% of TN participants had a baseline viral load >100 000 copies/mL, and 31% presented with advanced disease. Although these rates were much higher than in clinical trials with currently recommended first-line regimens, maintenance of viral suppression up to M24 was high and discontinuations due to virologic failure were rare in this group [24–29]. Despite less favorable viral and clinical characteristics of our study population, treatment outcomes aligned with clinical trials [2, 5, 6, 9], including virologic control and immunologic improvement (increase in CD4 cells) as well as drug safety/tolerability. In TAFNES, 96% of the M24 effectiveness set (M = E) had an HIV RNA level <50 copies/mL at M24, with a comparably high virologic effectiveness in participants with LD (95%); only 2% of the overall cohort had discontinued for virologic reasons. Other discontinuation reasons (13% of participants) were therapy simplification, patient decision and investigator discretion – perhaps influenced by newly available STR regimens (D/C/F/TAF: September 2017, B/F/TAF: June 2018).

The 2-year treatment persistence was high (81%); discontinuations were mainly driven by treatment simplification (4.4%), especially MTR to STR. In TAFNES, ADRs were reported in only 7% of the cohort and given as reasons for discontinuation in only 3.9%, including (≥2 participants) headache, diarrhea, depression and weight increase. No new safety signals emerged.

Regarding renal function, among TN participants the baseline CKD risk category (D:A:D score) was low in 78%, medium in 14% and high in 8%. In the TN group, a slight initial decrease in renal function parameters was observed, which subsequently stabilized, as has also been observed in clinical trials, and is consistent with the inhibition of tubular secretion of sCr associated with the inhibition of the renal transporters OCT2 or MATE1 by various antiretroviral drugs [30]. Rilpivirine, INSTI or cobicistat which were commonly used as part of first-line ART in the TAFNES population may have had an impact on this effect. These interactions can cause sCr increases and reductions in estimated, but not real, GFR [19]. Approximately 80% of TN participants in the TAFNES cohort received elvitegravir/cobicistat, rilpivirine or dolutegravir in addition to F/TAF.

In contrast to TN participants, baseline CKD risk among TE participants was low in only 36%, medium in 27% and high in 38%, highlighting the need for antiretroviral drugs with a good renal safety profile, considering an aging population on ART. In TE participants, renal function parameters remained relatively stable over time. These data support the European AIDS Clinical Society recommendation to use TAF particularly for PWH with coronary disease, osteoporosis or nephrotoxic comedication [31].

In addition to the UNAIDS 90-90-90 (more recently 95-95-95) targets, a 'fourth target' was suggested to ensure that 90% (or 95%) of PWH with viral suppression experience good HRQoL. This emphasizes PROs rather than just virologic outcomes and clinical terms [32]. Few PRO evaluations are available regarding F/TAF- or TAF-based ART: the DIAMOND study found increased satisfaction of TN subjects after being rapidly initiated on F/TAF-based ART with boosted darunavir. Another evaluation of two cross-sectional online surveys in pretreated and formerly ART-naïve PWH on darunavir/cobicistat/FTC/TAF showed a high and stable treatment satisfaction [33–35].

In the TAFNES cohort, TE participants were asked to report their treatment satisfaction in comparison to previous ART (HIVTSQc). Treatment satisfaction increased after switching, regardless of age, sex or treatment group. This finding confirms data on PROs from pivotal phase III RCTs for F/TAF-containing STRs [36]. Symptom distress as well as SF-36 MCS and PCS scores remained stable among TE participants, but improved significantly among TN. After 24 months, median scores of both the SF-36 MCS and PCS scores were above 50 in TN and TE, indicating that in the majority of participants the self-reported mental and physical health was above the average of a so-called normative population. In TN participants, median MCS and PCS scores were even higher than in TE participants and symptom distress (HIV-SI)

was lower, emphasizing the value of early treatment initiation and preventive strategies regarding HRQoL in aging PWH. Of note, in two other German HIV cohorts recruiting TN and TE PWH between 2018 and 2019, mean HIV-SI scores in TN and TE were in the same range [37, 38]. A comparison with even more patient groups is made difficult by the fact that the total HIV-SI scores are often not provided, since often only the bothersome count is shown or the results for single items.

Although interpretation of PROs may be limited by a potential selection bias in the TAFNES cohort (only participants who completed the respective questionnaires at baseline and during follow-up were included in these PRO analyses), these data on patient-reported outcomes are needed for better understanding PROs in comparison with other HIV populations and treatments. Health-related quality of life data are increasingly being taken into account in the assessments of treatment effects in the regulatory approval process. With this cohort we provide an overview of quantitative PRO measures in a cohort of PWH in Germany. PROs are a vital tool for capturing and amplifying patients' voices in clinical research and healthcare. They provide a direct channel for patients to share their experiences, preferences and concerns, ensuring that their perspectives are integral to medical decision-making and treatment development.

CONCLUSIONS

The non-interventional TAFNES cohort of 767 PWH analyzed F/TAF-based HIV-1 therapies such as E/C/F/TAF, R/F/TAF or F/TAF plus another 3rd agent in real-world clinical settings in Germany. The final data-cut at M24 demonstrated high treatment persistence, remarkably for the two single-tablet study groups, whereas new therapy simplification options probably resulted in a lower regimen persistence in the multiple-tablet arm. Although our study population presented with higher viral loads and more advanced disease, virologic outcomes were comparable to clinical trials with a high percentage for effectiveness and a low virologic failure rate (2%). Regimen persistence and virologic response was comparable for late-diagnosed participants.

Study drug discontinuations in this cohort were driven by new ART simplification options. There were <4% discontinuations due to drug-related adverse events, and no new safety concerns arised. Favorable PROs reflect high treatment satisfaction and good tolerability in a real-world setting outside of clinical trials. By incorporating PROs, healthcare providers and researchers can better understand the real-world impact of diseases and treatments from the patient's viewpoint, leading to

more patient-centered care and improved health outcomes.

AUTHOR CONTRIBUTIONS

CS: collection and analysis of data, drafting and reviewing article, approval of final MS for submission. CDS: collection and analysis of data, drafting and reviewing article, approval of final MS for submission. AR: collection and analysis of data, drafting and reviewing article, approval of final MS for submission. SC: collection and analysis of data, drafting and reviewing article, approval of final MS for submission. SM: collection and analysis of data, drafting and reviewing article, approval of final MS for submission. SS: analysis of data, drafting and reviewing article, approval of final MS for submission. BA: collection and analysis of data, drafting and reviewing article, approval of final MS for submission. MH: study design/conception, drafting and reviewing article, approval of final MS for submission. HR: study design/conception, collection and analysis of data, drafting and reviewing article, approval of final MS for submission. H-JS: study design/conception, drafting and reviewing article, approval of final MS for submission.

ACKNOWLEDGEMENTS

The authors thank the study sites and participants, MUC Research for medical writing support and Anna Chapman-Barnes (Aspire Scientific, Bollington, UK) for manuscript editing, funded by Gilead Sciences.

FUNDING INFORMATION

This TAFNES study was funded by Gilead Sciences. Funding for medical writing support for this article was provided by Gilead Sciences. The sponsor, Gilead Sciences, played a role in the study design, data collection and analysis, decision to publish and preparation of the manuscript.

CONFLICT OF INTEREST STATEMENT

CS reports speaker fees and/or advisory board membership from Gilead Sciences, Janssen-Cilag, MSD and ViiV healthcare; travel grants for scientific conference attendance from Gilead, Janssen, AbbVie. CDS reports grants and personal fees from AbbVie, Janssen-Cilag, MSD and ViiV Healthcare; grants, fees and non-financial support from Gilead Sciences; grants from Cepheid; personal fees from GSK – during the conduct of the study; fees from AstraZeneca; other from Apeiron; grants, personal fees and non-financial support from Braun Melsungen; grants and personal fees from BioNTech and Eli Lilly; personal fees from Eli Lilly, Formycon, Moderna, Molecular Partners, Novartis, Pfizer, Roche, Shionogi and SOBI; and travel grants from Copan. AR reports personal fees

and grants from AbbVie, Gilead, Janssen, MSD, ViiV and Tillotts. SC reports personal fees and grants from AbbVie, Gilead, Indivior, Janssen, MSD and ViiV. SM reports speaker fees and/or advisory board membership from AbbVie, Gilead, MSD and ViiV. SS, BA and MH are employees of Gilead Sciences GmbH and hold equity in Gilead. HR is an employee of Gilead Sciences Europe Ltd. and holds equity in Gilead. H-JS reports fees for advisory boards (ViiV Healthcare, MSD, Gilead Sciences); travel grants from Gilead Sciences and MSD; and speaker fees from Gilead, MSD and ViiV Healthcare.

DATA AVAILABILITY STATEMENT

Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Sciences' discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

ETHICS STATEMENT

This was an observational study. The ethics committees and competent authorities were notified of the cohort. All subjects gave informed consent prior to enrollment.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Stephan C, Spinner CD, Rieke A, et al. Effectiveness, safety, and patient-reported outcomes of emtricitabine/tenofovir alafenamide-based regimens for the treatment of HIV-1 infection: Final 24-month results from the prospective German TAFNES cohort study. *HIV Med.* 2025;26(2):239-251. doi:[10.1111/hiv.13728](https://doi.org/10.1111/hiv.13728)