Switch from tenofovir disoproxil fumarate (TDF)- to tenofovir alafenamide (TAF)-based regimens in clinical practice - Real-world data of the German PROPHET cohort study

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Background

PROPHET is a prospective, nationwide, 2-year, multicenter cohort study in chronically HIV-infected adults initiated on ART. Inclusion criterion was the use of a regimen recommended by treatment guidelines in Germany at study start in August 2014, i.e. tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI), an integrase inhibitor (INI) or a protease inhibitor (PI).

Primary objectives included pharmacoeconomic and clinical outcomes of different ART strategies.

During the study new antiretroviral options such as TAF-based fixed-dose combinations became available, namely elvitegravir/cobicistat/TAF/FTC (EVG/COBI/FTC/TAF; in 11/2015), FTC/TAF (in 04/2016), and rilpivirine/FTC/TAF (RPV/FTC/TAF; in 06/2016).

Here we focus on the characteristics and outcomes in PROPHET participants switched from TDF- to TAF-based ART.

Methods

Inclusion criteria

Adult, chronically HIV-infected patients of the PROPHET cohort who were switched from TDF- to TAF-based ART.

Variables of interest

- Prior antiretroviral regimen before switch to TAF-based ART and reason for switch
- Persistence of fixed-dose combination including TAF (using Kaplan-Meier analysis)
- Viral suppression (<50 copies/mL; on-treatment (OT) analysis and modified ITT (mITT) analysis, missing=excluded) and maintenance of viral suppression until last follow-up
- Health-related quality of life (HRQL) using validated questionnaires (at months 0, 12 and 24), i.e.
  - the ASDM (ACTG symptom distress module; 22 items, range 0-4, higher scores indicate more bothersome symptoms) and
  - the Short-Form 12 (SF-12) questionnaire reported as physical and mental component summaries (using norm based scoring; higher scores indicate higher HRQL).

Results

Patient characteristics and antiretroviral combinations

PROPHET included 444 patients (91% males) initiated on INI- (n=170, 84% DTG), NNRTI- (n=133, 95% RPV) or PI-based ART (n=141, 93% DRV).

FTC/TDF was used in 346 patients (78%). During the study, 150 patients (34% of the cohort; 91% males, 95% with HIV-RNA<50 cp/mL) were switched from TDF-based to TAF-based ART, i.e. FTC/TAF+3rd agent (n=58), RPV/FTC/TAF (n=51) and EVG/COBI/FTC/TAF (n=41). Prior regimens are shown in Table 1.

Primary reasons for switch (>5%) were prevention of renal/bone toxicity (51%), use of TAF as TDF successor drug (12%), adverse drug reactions (ADRs) on prior ART (10%), ART simplification (9%), and patient request (7%).

Table 1. Prior antiretroviral regimens and HIV-related characteristics of patients switched from TDF- to TAF-based ART

	Total (N=150)	FTC/TAF+ 3rd agent* (N=58)	RPV/FTC/TAF (N=51)	EVG/COBI/ FTC/TAF (N=41)
Male gender; N (%)	137 (91)	55 (95)	47 (92)	35 (85)
Age at switch, years, median (IQR)	43 (34-51)	45 (34-53)	42 (35-50)	40 (33-50)
TDF-based ART prior to switch				
RPV/FTC/TDF	(n=55)	-	50 (91%)	5 (9%)
TDF/FTC+DRV/RTV (or COBI)	(n=40)	25 (63%)	-	15 (38%)
FTC/TDF+DTG	(n=32)	28 (88%)	1 (3%)	3 (9%)
EVG/COBI/FTC/TDF	(n=17)	-	-	17 (100%)
Other	(n=6)	5 (83%)	-	1 (17%)
CDC stage C prior to switch, N (%)	20 (13)	14 (24)	3 (6)	3 (7)
CD4 cell count prior to switch, cells/µL, median (IQR)	586 (416-780)	491 (360-757)	674 (530-880)	586 (392-756)
CD4 cell count prior to ART initiation, cells/µL, median (IQR)	386 (230-566)	306 (161-468)	479 (335-638)	367 (154-529)
HIV-1 RNA <50 cp/mL prior to switch, N (%)	142 (95)	54 (93)	51 (100)	37 (90)
HIV-1 RNA >100,000 prior to ART initiation, N (%)	54 (36)	32 (55)	9 (18)	13 (32)
Late presentation at ART initiation, N (%)**	70 (47)	36 (62)	14 (27)	20 (49)

IQR: interquartile range; *other than RPV or EVG/COBI; **CD4 <350 cells/µL and/or CDC stage C;

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Treatment persistence and retention in the study

Until study end, 7 patients (5%) discontinued TAF-based regimens for the following reasons.

- 4 patients due to ADRs (3%), i.e.
  - n=1 gastrointestinal ADR (FTC/TAF+DTG)
  - n=1 renal ADR (EVG/COBI/FTC/TAF; documented chronic renal diseases prior to switch)
  - n=2 ADRs classified as ′other′, i.e. ′intolerance with suspected tinnitus′ (while on FTC/TAF+DTG) and ′back pain′ (RPV/FTC/TAF)
- 1 patient due to strategic reasons “simplification” (RPV/FTC/TAF)
- 1 patient due to drug-drug interaction (RPV/FTC/TAF)
- 1 patient due to other strategic reason “not specified” (FTC/TAF+DRV/r)

In addition, 4 study discontinuations unrelated to the use of TAF-based ART were reported (2x change in physician, 1x death, 1x loss to follow-up).

Overall, Kaplan-Meier estimates of persistence on TAF at months 6, 12 and 18 were 96%, 92% and 92%, respectively. For persistence on EVG/COBI/FTC/TAF, FTC/TAF and RPV/FTC/TAF see Figure 1.

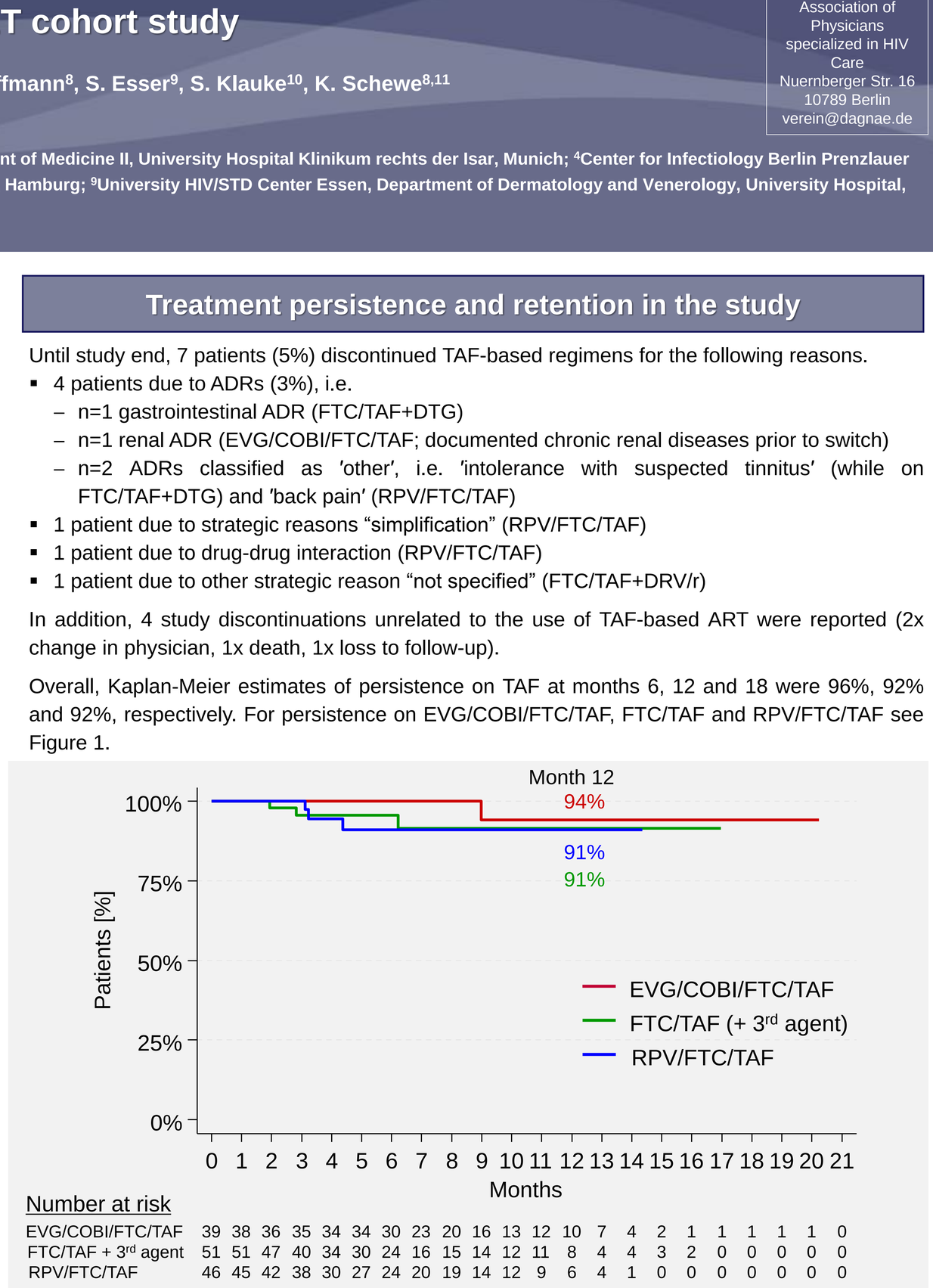

Figure 1. Kaplan-Meier-analysis: Time on fixed dose combination including TAF

Virologic effectiveness

At last follow-up, after a median of 7.6 months on TAF-based ART (IQR 4.9-11.9, max. 20.3), HIV-RNA levels were <50 cp/mL in 91% of patients in OT analysis and in 87% of patients in mITT (missing=excluded) analysis. 95% of patients with <50 cp/mL prior to switch (114/120) maintained viral suppression after switch (OT analysis). Viral suppression for FTC/TAF+3rd agent, RPV/FTC/TAF and EVG/COBI/FTC/TAF is shown in Table 2.

Table 2. Virologic suppression at last follow-up	Total	FTC/TAF+ 3rd agent	RPV/FTC/ TAF	EVG/COBI/ FTC/TAF
HIV-1 RNA <50 cp/mL, on treatment, N (%)	115/126 (91)*	41/48 (85)	40/41 (98)	34/37 (92)
HIV-1 RNA <50 cp/mL, mITT, missing=excluded, N (%)	115/132 (87)	41/51 (80)	40/43 (93)	34/38 (89)

50-199 cp/mL: 7/126 (5.6%); 200-999 cp/mL: 3/126 (2.4%); ≥1000 cp/mL: 1/126 (0.8%)

Health-related quality of life (HRQL)

Overall, HRQL improved after ART initiation and remained relatively stable in patients switched to TAF-based ART after month 12.

ASDM (ACTG symptom distress module) and SF-12 physical and mental component summary scores did not change significantly between months 12 and 24 in patients switched to TAF-based ART after month 12 (see Table 3; based on observed data).

Table 3. HRQL	Month 12	Change from month 12 to 24
ASDM score, mean (standard derivation, SD)	14.1 (12.7) (n=100)	+0.8 (8.5) (n=88)
SF-12 physical component summary, mean (SD)	50.4 (8.8) (n=100)	+0.3 (7.7) (n=87)
SF-12 mental component summary, mean (SD)	49.4 (10.5) (n=100)	-1.3 (10.6) (n=87)

Conclusion

- With the introduction of TAF-based regimens, one-third of patients included in the observational PROPHET study were switched from TDF- to TAF-based ART.
- The main reason for switch was prevention of renal and bone toxicity.
- Experience from clinical trials concerning treatment retention, safety and efficacy was confirmed in this cohort with a low rate of TAF discontinuations due to ADRs and maintenance of viral suppression in 95% of patients.

Participating centers and organizations

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