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

M. Bickel1, Ch. Weyer1, Ch. Spieker2, A. Baumgarten1, H. Jaeger1, N. Postel1, E. Wolf1, Ch. Hoffmann1, S. Esser1, S. Klaue1, K. Schewe1

for the PROPHET study group of dagnea e. V.

1Institut für klinische Pharmakologie, Frankfurt: Private Praxis Elbepaltz, Dr. Krumeier/1993/2041/2047
2Cologne: Department of Medicine II, University Hospital Klinikum rechts der Isar, Munich; Center for Infectiology Berlin Freunde
3Berg GmbH (Zib; Berlin); 4MIZ Karlsbad, Munich; 5Prisma, Munich; 6MUC Research, Munich; 7CIY Studiencenter, Hamburg; University HIV/STD Center Essen, Department of Dermatology and Venereology, University Hospital, Essen; 8Institut für klinische Pharmakologie, Frankfurt: a.s. e.V., Berlin; all Germany

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/entecavir (TDF-FTC) or abacavir/lamivudine (ABC/3TC) plus another 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 several antiretroviral options such as TAF-based fixed-dose combinations became available, namely elvitegravir/cobicistat/TAF-FTC (EVG/CObI/TAF-FTC; in 11/2015), TAF-FTC (in 04/2016, and riprafenine/TAF-FTC [RPV/FTC/TAF; in 06/2016].

Here we focus on the characteristics and outcomes in patients 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)
• Virological response (≤50 copies/mL), on treatment (OT) analysis and modified ITT (mITT) analysis, missing-excluded and attainment of viral suppression following last up to follow
• Health-related quality of life (HRQL) using validated questionnaires (at months 0, 12 and 24, i.e.
  - the ASMD (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 (n=170, 84% DTG), NNRTI- (n=133, 95% RPV) or PI-based ART (n=141, 93% DRV).

TAF-FTC was used in 246 patients (78%). During the study, 150 patients (34% of the cohort; 91% males, 95% HIV-naive patients) were switched to TAF-based ART, i.e. TAF/FTC/3rd agent (n=58), RPV/FTC/TAF (n=51) and EVG/CObI/TAF/F (n=41). Prior regimens are shown in Table 1.4

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=105)</th>
<th>TDF/FTC+ 3rd agent</th>
<th>RPV/FTC/TAF</th>
<th>EVG/CObI/TAF/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/gender N (%)</td>
<td>137 (91)</td>
<td>56 (45)</td>
<td>47 (60)</td>
<td>30 (35)</td>
</tr>
<tr>
<td>Age at switch, years, median (IQR)</td>
<td>43 (34-51)</td>
<td>43 (34-50)</td>
<td>42 (35-50)</td>
<td>40 (33-50)</td>
</tr>
<tr>
<td>TDF-based ART prior to switch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPV/FTC/TDF</td>
<td>(n=55)</td>
<td>-</td>
<td>50 (91%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>TDF/FTC/DRV/abacavir</td>
<td>(n=40)</td>
<td>25 (63%)</td>
<td>-</td>
<td>15 (38%)</td>
</tr>
<tr>
<td>TDF/FTC/DTG</td>
<td>(n=32)</td>
<td>28 (88%)</td>
<td>1 (3%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>EVG/CObI/TAF/F</td>
<td>(n=17)</td>
<td>-</td>
<td>-</td>
<td>17 (100%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (43%)</td>
<td>3 (40%)</td>
<td>2 (33%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

CDC stage C prior to switch, N (%) | 20 (13) | 14 (24%) | 3 (6) | 0 (0) |

CD4 cell count prior to switch, cells/µL, median (IQR) | 516 (418-760) | 491 (362-575) | 674 (500-880) | 536 (376-756) |

CD4 cell count prior to ART initiation, cells/µL, median (IQR) | 386 (236-506) | 306 (167-460) | 479 (363-633) | 156-429 |

HIV RNA <50 copies/mL, prior to switch, N (%) | 142 (95) | 54 (93) | 51 (100) | 51 (100) |

HIV RNA >100,000 copies/mL, prior to ART initiation, N (%) | 54 (36) | 32 (56) | 9 (18) | 13 (22) |

Late presentation at ART initiation*, N (%) | 78 (47) | 36 (62) | 14 (25) | 20 (46) |

* IQR: interquartile range, “other than RPV or EVG/CObI” := CDC ≤500 cells/µL and/or CDC stage C.

We thank all participating patients as well as the staff and investigators of the study. Financial support for the conduct of the PROPHET cohort study was provided by Janssen-Cilag. Gilead Sciences provided financial support for the sub-analysis regarding the switch to TAF-based ART.

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/TAFT/DG)
  - 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/TAFT/DG) 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)

In addition, 4 study discontinuations unrelated to the use of ART were reported (2x change in treatment, 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 persisters on EVG/CObI/FTC/TAF and RPV/FTC/TAF see Figure 1.

Virologic effectiveness

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

Table 2. Virologic suppression at last follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N (%)</th>
<th>FTC/TAFT+ 3rd agent</th>
<th>RPV/FTC/TAF</th>
<th>EVG/CObI/TAF/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA ≤50 copies/mL, on treatment, N (%)</td>
<td>115/126 (91)</td>
<td>114/126 (90)</td>
<td>107/124 (86)</td>
<td>36/37 (98)</td>
</tr>
<tr>
<td>HIV RNA ≤50 copies/mL, mITT, missing-excluded, N (%)</td>
<td>115/132 (87)</td>
<td>114/132 (86)</td>
<td>107/124 (86)</td>
<td>36/37 (98)</td>
</tr>
</tbody>
</table>

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.

ASMD (ACTG symptom distress module) and SF-12 physical and mental component summary scores did not significantly differ 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Month 12</th>
<th>Change from month 12 to 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMD score, mean (standard deviation, SD)</td>
<td>14.1 (7.2) (n=107)</td>
<td>13.6 (7.0) (n=107)</td>
</tr>
<tr>
<td>SF-12 physical component summary, mean</td>
<td>50.4 (8.8) (n=103)</td>
<td>49.9 (9.0) (n=103)</td>
</tr>
<tr>
<td>SF-12 mental component summary, mean</td>
<td>49.2 (10.5) (n=103)</td>
<td>48.7 (10.6) (n=103)</td>
</tr>
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</table>

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.