Providing evidence from real world data – 3-year follow-up of Dolutegravir-based regimens in routine clinical care in Germany: the final analysis of the DOL-ART cohort

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Background

DOL-ART is a prospective, 3-year observational German cohort study in patients (pts) initiated on Tivicay (Dolutegravir, DTG)-based ART.

The study goal is to provide insights into real-life effectiveness, safety and health care resource utilization in a clinical routine setting in Germany.

Methods

Study population

- Adult HIV-1 infected pts on DTG-based ART for ≥4 weeks at time of enrollment

Primary and secondary objectives

- Frequency and type of monitoring measures for patient management
- Persistence of DTG-based regimens, reasons for DTG discontinuation
- Virological effectiveness of DTG-based ART (virologic response defined as HIV-1 RNA level <50 cp/mL, using ITT and on-treatment analysis)
- Incidence of serious adverse events (SAEs), serious and non-serious adverse drug reactions (SADRs, ADRs); AE reporting was not part of the eCRF.

Results

Study population

N=410 pts were included in DOL-ART between March and May 2014.

Table 1. Baseline characteristics	Overall (N=410)	ART-naïve (N=99, 24.1%)	Pre-treated (N=311, 75.9%)
Sex, male, n (%)	357 (87.1)	89 (89.9)	268 (86.2)
Age, years, median (IQR*)	45 (36 – 52)	39 (32 – 48)	46 (38 – 53)
Age >50 years, n (%)	116 (28.3)	11 (11.1)	105 (33.8)
CDC stage C, n (%)	95 (23.2)	10 (10.1)	85 (27.3)
HIV-1 RNA, median (IQR)	1.7 (1.7 - 4.1)	4.6 (4.1 – 5.1)	1.7 (1.7 – 1.7)
<50 cp/mL, n (%)		---	224 (72.0)
≥100,000 cp/mL, n (%)		26 (26.3)	---
CD4 cell count, median (IQR)	539 (348-766)	377 (245 – 549)	584 (422 – 800)
<200 cells/µL, n (%)	41 (10.0)	18 (18.2)	23 (7.4)
Most common antiretroviral combination partners (>5%), n [%]			
abacavir/lamivudine (ABC/3TC)	163 (39.8)**	53 (53.5)	110 (35.4)
tenofovir/emtricitabine (TDF/FTC)	196 (47.8)**	46 (46.5)	150 (48.2)

*IQR, interquartile range; ** triple ART with DTG+ABC/3TC in 39.5% and with DTG+TDF/FTC in 45.1%*

Reason for switch to DTG-based ART

Main reasons for switch were (multiple responses permitted): side effects on previous ART (31.8%), ART simplification (30.2%), patient wish (24.8%), comorbidities/concomitant medication (12.2%), and virologic failure (9.3%).

Comorbidities and comedication at baseline

Comorbidities were documented in 55.6% of pts (ART-naïve: 35.4% , pre-treated: 62.1%). Concomitant medication was documented in 35% of pts (ART-naïve: 24.2%, pre-treated: 36.3%).

Table 2a. Comorbidites (>5%) at baseline	n (%)
Depression	120 (29.3)
Hypertension	64 (15.6)
Cardiovascular diseases	39 (9.5)
Dyslipidemia (requiring treatment)	30 (7.3)
Pulmonary disease	28 (6.8)
Chronic HCV-infection	24 (5.9)

Table 2b. Comedication (>5%) at baseline	n (%)
Antihypertensive	66 (16.1)
Antidepressants	43 (10.5)
Prophylaxis/treatment of opportunistic infections	23 (5.6)

Monitoring

- The median number of visits to HIV specialists were 4.5 (IQR 4.2 - 5.1) per patient year (PPY).
- Referrals to specialists (excl. infectiologists) were reported in 74.1% of pts with a median of 1.0 referrals (IQR 0.7 - 1.8) PPY.

Table 3. Monitoring measures PPY	Median (IQR)
HIV-RNA/CD4 cell count	3.9 (3.4 – 4.2)
Blood count	4.0 (3.5 – 4.3)
Serum chemistry	4.0 (3.5 – 4.3)
Urine tests	1.0 (0.0 – 2.9)
Microbiological tests (includ. one or multiple tests)	0.7 (0.0 – 2.0)

Patient disposition after 3-year follow-up

Median observation time was 34.8 months with 72.0% of patients remaining under observation for 3 years.

Reasons for study discontinuation

- For 28.0% of pts (115/410) premature study discontinuation was reported.
- Reasons for *study* discontinuation were (multiple responses permitted):
  - Discontinuation of DTG (n=58/410; 14.1%) (for specific reasons, see Fig. 1)
  - Patient decision/withdrawal of consent (n=26; 6.3%)
  - Loss to follow-up (n=35; 8.5%), death (n=4; 1.0%; not reported as related to DTG), and other reasons (n=13; 3.1%)

Figure 1. Documented reasons for DTG discontinuation (n=58) (multiple responses permitted)

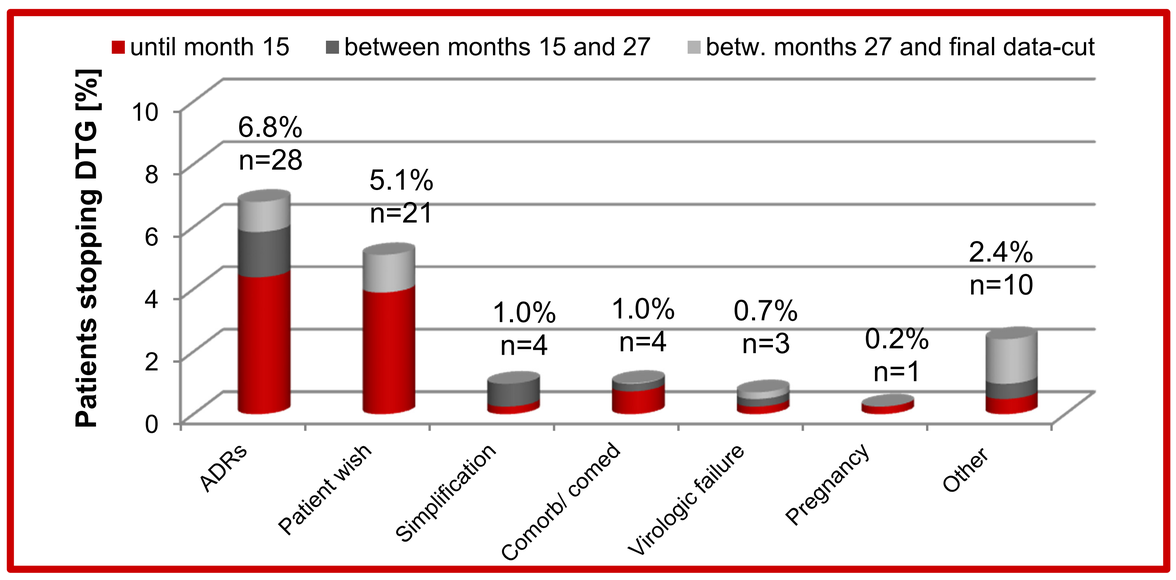

Table 4. ADRs leading to DTG discontinuation (≥ 1 event per patient)	n	%
Insomnia / sleeping disorders / fatigue	9	2.2
Depression / mood disorder	6	1.5
Gastrointestinal ADR	6	1.5
Liver-related ADR	4	1.0
CNS-related ADR (forgetfulness / vertigo)	2	0.5
Skin disorder	2	0.5
Sexual dysfunction	3	0.7
Other	8	2.0

ADRs, SADRs and SAEs

In total, 256 events (123 ADRs, 2 SADRs, 131 SAEs) were reported, resulting in an event rate of 0.25 PPY.

- Overall, 18.3% of pts (75/410) experienced 125 ADRs (incl. 2 SADRs*).
  - * increase of hepatic enzymes, grade 4, with recovery upon withdrawal of DTG, and lateral hypercompression syndrome of the knee (requiring hospitalization)
- Of ADRs, 66.4 %, 16.8% and 8.0% occurred in years 1, 2, 3, respectively.

Virological effectiveness

- At last follow-up (>month 33), HIV-RNA level was <50 cp/mL in 67.8% of the study population (ITT, discontinuation/missing =failure) (ART-naïve: 71.7%, pre-treated: 66.6%).
- Of pts under follow-up until final analysis, HIV-RNA was <50 cp/mL (≤200 c/mL) in 88.3% (94.9%) (on-treatment analysis).
- In 3 pts (0.7%), DTG was discontinued due to virologic failure (i.e. confirmed HIV-RNA>1,000 cp/mL after switch from failing RAL+LPV/r to DTG+LPV/r and after switch from ABC/3TC+RAL (with low level viremia (LLV) at baseline) to DTG+ABC/3TC, and confirmed LLV >50-200 cp/mL after switch from suppressive TDF/FTC/EFV to TDF/FTC+DTG; with no further information on INSTI resistance)

Conclusions

- During the course of this 3-year cohort, monitoring measures were mainly related to routine quarterly controls of HIV-disease, reflecting local HIV treatment guidelines.
- DTG discontinuation rates due to ADRs or virologic failure were low with 6.8% and 0.7%, respectively – showing a good safety profile and good virologic effectiveness of DTG use in clinical routine.
- Moreover, ADR rates were observed to decrease over time.

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