Tolerability and persistence of dolutegravir-based regimens: Second interim analysis of the prospective multicenter DOL-ART cohort

PE 9/52

Bohr U[1], Bickel M[2], Hegener P[3], Hillenbrand H[4], Kuhlmann B[5], Pauli R[6], Mayr C[7], Wuensche T[8], Lüftenegger D[9], Sych M[10], Westermayer B[10], Walli RK[9]

[1]Praxiszentrum Kaiserdamm, Berlin; [2]Infektiologikum, Frankfurt; [3]MVZ Düsseldorf; [4]Praxis City Ost, Berlin; [5]Praxis Georgenstraße, Hannover; [6]Isarpraxis, Munich; [7]MVZ Finnländische Straße, Berlin; [8]Praxis Wuensche, Berlin; [9]ViiV Healthcare, Munich; [10]GlaxoSmithKline, Munich

Background

DOL-ART is a prospective, 3-year observational German cohort study in patients initiated Tivicay (Dolutegravir, DTG)-based ART ≥4 weeks prior to study enrolment. The study goal is to provide insights into real-life effectiveness, safety and health care resource utilization in a clinical routine setting.

Methods

Study population

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

Primary and secondary objectives

- Frequency and type of monitoring measures (including laboratory tests and referrals to specialists) while on DTG-based ART (primary outcome)
- Virological effectiveness of DTG-based ART (virologic response defined as HIV-1 RNA level <50 cp/mL, using on-treatment analysis)
- Incidence of adverse drug reactions (ADRs)
- Persistence of DTG-based regimens, reasons for DTG discontinuation

Here we compare the results of the 2nd interim analysis (data-cut 27 months after last-patient-in (LPI)) with the first interim analysis (15 months after LPI).

Results

Study population

N=411 patients were included in DOL-ART between March and May 2014. Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics

	Overall (N=411)	ART-naïve (N=99, 24.1%)	Pre-treated (N=312, 75.9%)
Sex, male, n (%)	357 (86.9)	89 (89.9)	268 (85.9)
Age, years, median (IQR*)	45 (36 – 52)	39 (32 – 48)	46 (38 – 53)
Age >50 years, n (%)	115 (28.0)	11 (11.1)	104 (33.3)
CDC stage C, n (%)	96 (23.4)	10 (10.1)	86 (27.6)
HIV-1 RNA, median (IQR*)	1.7 (1.7 - 4.1)	4.7 (4.1 – 5.1)	1.7 (1.7 – 1.8)
<50 cp/mL, n (%)		---	224 (71.8)
≥100,000 cp/mL, n (%)		26 (26.3)	---
CD4 cell count, median (IQR)	537 (345-765)	377 (245 – 549)	584 (422 – 800)
<200 cells/µL, n (%)		18 (18.2)	23 (7.4)
Most common antiretroviral combination partners [%]			
abacavir/lamivudine (ABC/3TC)	39.9**	53.5	35.6
tenofovir/emtricitabine (TDF/FTC)	47.9**	46.5	48.4

**IQR, interquartile range;*
*** triple ART with DTG+ABC/3TC in 39.7% and with DTG+TDF/FTC in 45.3%*

Comorbidities at baseline

Relevant comorbidities were reported in 55.5% of patients (n=228/411; most common (≥10%): depression (29.2%; ART-naïve: 16.2%, pre-treated: 33.3%) and hypertension (15.6%, ART-naïve: 6.1%, pre-treated: 18.6%)).

Observation time

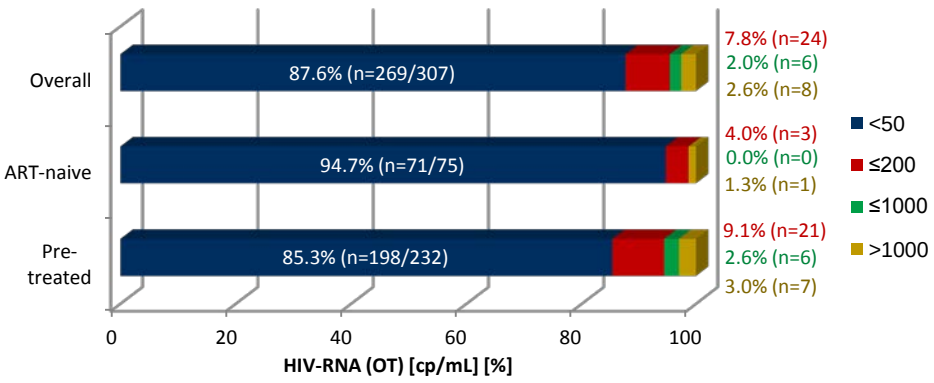
Median observation times until 1st and 2nd data-cut were 15.8 months (IQR 15.2 - 16.8) and 27.8 months (IQR 27.1 - 28.7), respectively, with 86.4% and 78.6% of patients remaining under observation.

Persistence of DTG-based regimens during follow-up

Until 2nd data-cut, in 56.4% of patients (232/411) the DTG-based regimen remained unchanged; 30.4% of patients (125/411) were switched to Triumeq, a onepill-Regimen consisting of DTG/ABC/3TC (39.4% of ART-naïve, 27.6% of pre-treated patients). At last follow-up, other common combination partners of DTG were TDF/FTC (36.7%; n=151/411) and ABC/3TC (13.6%; n=56/411).

Virological response

Figure 1. Virological response of patients under follow-up until the 2nd data cut (on-treatment analysis, last observation carried forward between month 21 and 27)



Monitoring

- The median numbers of documented physician visits until 1st and 2nd data-cut were 4.6 (IQR 3.9 - 5.4) and 4.3 (IQR 3.7 - 5.0) per patient year (PPY), respectively.
- Monitoring measures per patient year are shown in Table 2.
- Referrals to specialists were documented in 68.6% of patients (n=282/411) (62.6% of ART-naïve (n=62/99), 70.5% of pre-treated (220/312)). In patients referred to medical specialists, the median number of visits was 1.2 PPY (IQR 0.8-1.8).

Table 2. Monitoring measures

Monitoring measures per patient year (PPY) Median (IQR)	Until 1st data-cut	Until 2nd data-cut
Overall	13.7 (10.5 – 17.4)	13.7 (10.5 – 17.3)
HIV-RNA/ CD4 cell	3.5 (2.9 – 4.0)	3.5 (2.9 – 4.0)
Blood count	3.6 (3.0 – 4.1)	3.7 (2.9 – 4.1)
Serum chemistry	3.6 (3.0 – 4.2)	3.7 (3.0 – 4.1)
Urine tests	0.8 (0.0 – 2.8)	0.8 (0.0 – 2.6)
Microbiological tests (including one or multiple tests)	0.7 (0.0 – 1.5)	0.4 (0.0 – 1.7)

Reasons for study discontinuation

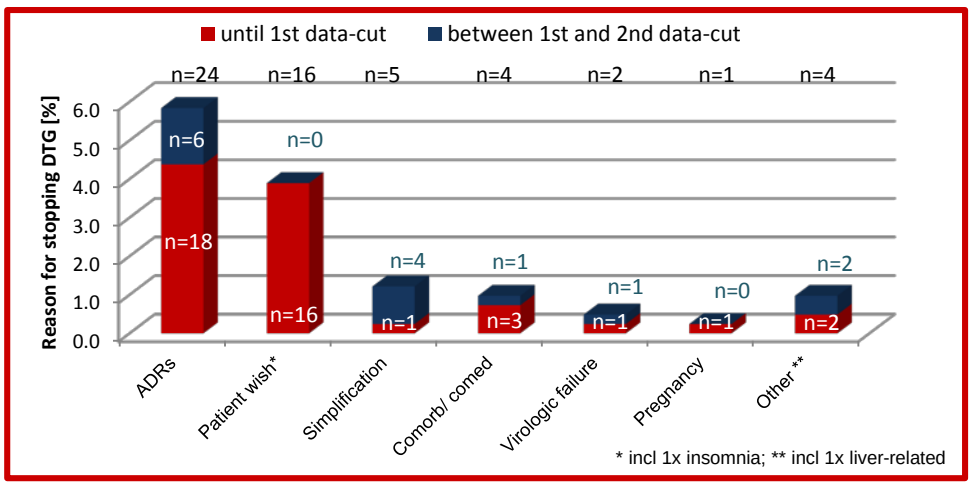
- N=88/411 (21.4%) discontinued from the study until the 2nd data cut (N=56/411 (13.6%) until the 1st data cut).
- Reasons for study disc. were (multiple responses permitted):
  - discontinuation of DTG (n=47/411; 11.4%) (see Figure 2)
  - patient decision/withdrawal of consent (n=19/411; 4.6%)
  - loss to follow-up (n=20/411; 4.9%), death (n=2/411; 0.5%), and other reasons (n=13/411; 3.2%)

Table 3. ADRs leading to discont. of DTG until 1st and between 1st and 2nd data-cut (≥ 1 event per patient)

ADR	n	%	n	%
Insomnia / Sleeping disorders/ Fatigue	6	1.5	1	0.2
Depression / Mood Disorder	5	1.2	0	0.0
Gastrointestinal	4	1.0	1	0.2
Liver-related	3	0.7	1	0.2
CNS*	1	0.2	1	0.2
Skin disorder	1	0.2	1	0.2
Sexual dysfunction	1	0.2	1	0.2
Other**	4	1.0	3	0.7

*forgetfulness, vertigo **arthralgia, psychosomatic symptoms, heart palpitation, hypercholesterinemia, headache, indisposition and weight gain

Figure 2. Documented reasons for discontinuation of DTG (n=47) (multiple responses permitted)



Adverse drug reactions (ADRs)

- 17.0% of patients (70/411) experienced ADRs until the 2nd data-cut (covering a median observation time of 27.8 months).
- Discontinuation of DTG due to ADRs was reported in 5.8% of patients, incl. 1.2% for depression (see Fig. 2, Table 3), only occurring before 1st data-cut.
- One patient experienced an SADR (grade 4 increase of hepatic enzymes (13 months after DTG start) with recovery after withdrawal of DTG.
- Cumulative ADR incidences per year were 12.7% (52/411) in the first and 3.0% (11/361) in the second year. The overall ADR rate was 0.33 PPY in the first and 0.11 PPY in the second year.

Conclusions

- In this real-life cohort of ART-naïve and pre-treated patients on DTG-based ART, monitoring measures were mainly related to routine quarterly controls of HIV-disease.
- After a median observation time of 27.8 months, DTG discontinuation rates due to ADRs or virologic failure were low with 5.8% and 0.5%, respectively.
- Overall ADR rates markedly decreased from the first to the second year.

Acknowledgments

We thank all the participating patients and investigators of the DOL-ART cohort. Support in medical writing was provided by MUC Research GmbH. The study is sponsored by ViiV Healthcare, Germany.