Real-world Data From the Prospective, Multicenter Study on the Use of Dolutegravir-Based Regimens (DBR) in ART-Naive and Experienced People Living With HIV: 12-Months Results From the Russian TESLA Study

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Sergey Kuznetsov,[1] Stella Minaeva,[2] Natalia Sizova,[3] Firaya Nagimova,[4] Elena Orlova-Morozova,[5] Margarita Radzikhovskaya,[6] Valeriy Shevchenko,[7] Andres Maldonado,[8] Bryn Jones[9]

[1]GSK, Medical Affairs, Moscow, Russian Federation; [2]Nizhny Novgorod Regional Centre for AIDS and Infectious Diseases Prophylaxis and Control, General, Nizhny Novgorod, Russian Federation; [3]Centre for AIDS and Infectious Diseases Prophylaxis and Control, General, St. Petersburg, Russian Federation; [4]Tatarstan Republican Centre for AIDS and Infectious Diseases Prophylaxis and Control, General, Kazan, Russian Federation; [5]Moscow Regional for AIDS and Infectious Diseases Prophylaxis and Control, General, Moscow, Russian Federation; [6]Regional Centre for AIDS and Infectious Diseases Prophylaxis and Control, General, Chelyabinsk, Russian Federation; [7]Altai Regional Centre of AIDS and Infectious Diseases Prophylaxis and Control, General, Barnaul, Russian Federation; [8]ViiV Healthcare, Global Medical Affairs, Wavre, Belgium; [9]ViiV Healthcare, Global Medical Affairs, Brentford, UK

Key Takeaways

- **The aim of the study was to describe the real-world data of DBR use in Russia**
- **The use of DTG-based regimens in this real-world Russian TESLA cohort was associated with a high level of effectiveness and safety through 12 months**

Introduction

- ART-related long-term toxicities remain a topic of interest. Considering that ART is life-long, reasons for therapy discontinuation and switching regimens need further investigation in large epidemiologic studies.
- Russia has the largest HIV epidemic in Europe and Central Asia with a small downward trend in new HIV infections [1]. 56.9% of all people living with HIV (PLHIV) in Russia were infected through drug use [2].
- TESLA is the first prospective real-world data study evaluating the effectiveness and long-term safety of using DBRs in both ART-naive and experienced PLHIV in Russia, including key affected populations (including drug users: intravenous and synthetic).
- Here we present the study baseline characteristics and Month 12 outcomes.

Methods

- TESLA is a prospective, non-interventional, 3-year study of 1000 PLHIV who started taking DBRs from May to October 2020 (study initiation time) in 14 Russian centres.
- Study data was collected during visits in accordance with routine clinical practice. Each participant in the study was observed until dolutegravir (DTG) was discontinued, death, loss of contact, or the end of data collection.
- No additional visits or procedures are mandated per protocol. The visits of PLHIV take place approximately every 3-6 months and allowed time windows were ±2 months for Month 12 full analysis set (FAS).
- PLHIV with any prior use of DTG or history of virologic failure on any integrase strand transfer inhibitors (INSTI) were not eligible to enter the study.

Outcomes:

- Proportion of participants discontinued or switched from DTG;
- Reasons for discontinuation;
- Time to discontinuation of DTG (estimated using Kaplan-Meier analysis);
- Proportion of participants with virologic suppression (viral load <250 cp/mL); proportion of participants with low-level viremia (viral load >250 cp/mL and <500 cp/mL); proportion of participants with virologic rebound (two consecutive measurements of viral load ≥500 cp/mL after previously achieved suppression <250 cp/mL); proportion of participants with non-response (two consecutive measurements of viral load ≥250 cp/mL after at least 6 months of treatment);
- CD4+ cell count change from baseline;
- Proportion and frequency of adverse drug reactions (ADRs) deemed related to DTG and serious adverse events (SAEs), including pregnancy outcomes, whether related or not to DTG;
- Reasons for administration/switching to DTG-based regimen at baseline (investigator-reported for ART-experienced PLHIV according to the pre-specified groups – toxicity or ineffectiveness of the previous regimen and other).

Results

Study Population

- 982 PLHIV were included in the FAS for 12 months. 18 participants were not included as their data were not fully verified.
- Baseline characteristics are shown in Table 1.
  - Overall, 81% were ART-experienced, 27% were on a two-drug regimen, 56% were male, median age was 40 years, median body mass index (BMI) was 24 kg/m^2. The mean time (±SD) since HIV diagnosis was 6.5±5.7 years; absolute values ranged from 0.0 to 23.9 years.
  - Baseline HIV-1 RNA was <250 cp/mL in 83% and CD4+ cell count was ≥200 cells/μL in 91% of ART-experienced PLHIV.
  - In ART-naive PLHIV, 26% had viral load ≥100,000 cp/mL and 77% had CD4+ counts ≥200 cells/μL at baseline.
  - Of ART-experienced participants, regimen prior to switch contained an NNRTI, PI and INSTI in 57%, 47% and 2%, respectively.
- Additional subpopulations for the purpose of exploratory sub-analysis were identified: participants on DTG + lamivudine (3TC) - 2DR (n=269) and 3DR (n=708).
  - 32.4% (258/797) of ART-experienced and 5.9% (11/185) of ART-naive PLHIV were included in the 2DR subgroup. 5 participants were not included in either subgroup as they did not match the criteria.
- Comorbidities (>2.5%) at baseline were detected in 645/982 (65.7%) PLHIV:
  - Liver diseases - 38.4% (HCV - 35.3% and HBV - 2.5%)
  - Obesity - 16.2% and metabolic disorders - 12.6%
  - Hypertension - 6.5%
  - Other viral infections - 5.8%
  - CVD - 3.2%, bone disorders - 2.5%

Table 1. Baseline Characteristics

	ART-experienced (n=797)	ART-naive (n=185)
Sex, male, n (%)	458 (57.5%)	110 (59.5%)
Age ≥50 years, n (%)	86 (10.8%)	30 (16.2%)
Drug users, n (%)	121 (15.2%)	19 (10.3%)
Intravenous drug users	120 (15.1%)	18 (9.7%)
HIV-1 RNA >100,000 cp/mL, n (%)	16 (2.0%)	49 (26.5%)
HIV-1 RNA <250 cp/mL, n (%)	660 (82.8%)	0
CD4+ count, cells/μL, median (IQR)	429 (231 - 580)	573 (386 - 765)
<200 cells/μL, n (%)	62 (7.8%)	38 (20.5%)
Comorbidities >2, n (%)	33 (4.1%)	10 (5.4%)

IQR: interquartile range.

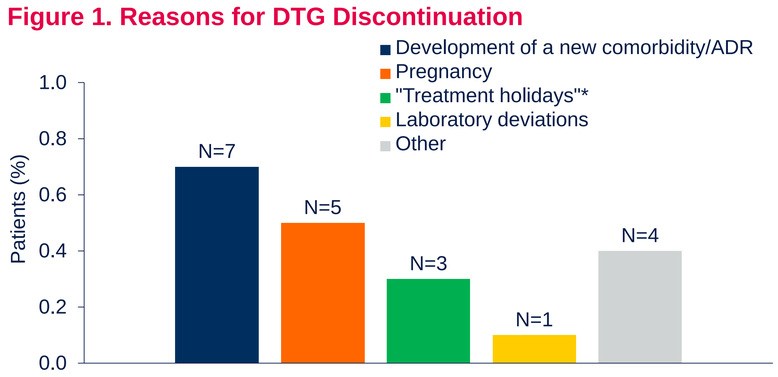
Reasons for Administration/Switching to DBR

- The majority of investigators (73.4%) reported “other” as the main reason. Of these, 45.9% (269/585) due to regimen optimization.
- Toxicity of the previous regimen - 161/797 (20.2%)
- Ineffectiveness of the previous regimen - 51/797 (6.4%)

Reasons for Study Discontinuation

- Nine percent of PLHIV (92/982) discontinued the study; main reasons were loss of contact (6.0%), discontinuation of DTG (2.0%, n=20; 3 [1.1%] in 2DR and 17 [2.4%] in 3DR subgroups), death (0.7%) and physician’s decision (0.3%).
- Reasons for DTG discontinuation are shown in Figure 1.

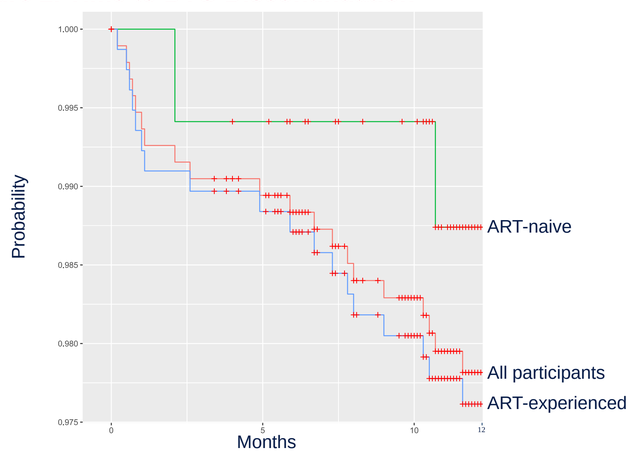
Figure 1. Reasons for DTG Discontinuation



*ART interruption for ≥45 days.

- Kaplan-Meier median estimate of the time to DTG discontinuation was not possible due to the small number of discontinuations. The median time to DTG discontinuation reported was only for discontinued patients, not for the study population. The median time to DTG discontinuation was 5.4 months for FAS and ART-experienced and 6.4 months for ART-naive participants (Figure 2).

Figure 2. Time to DTG Discontinuation



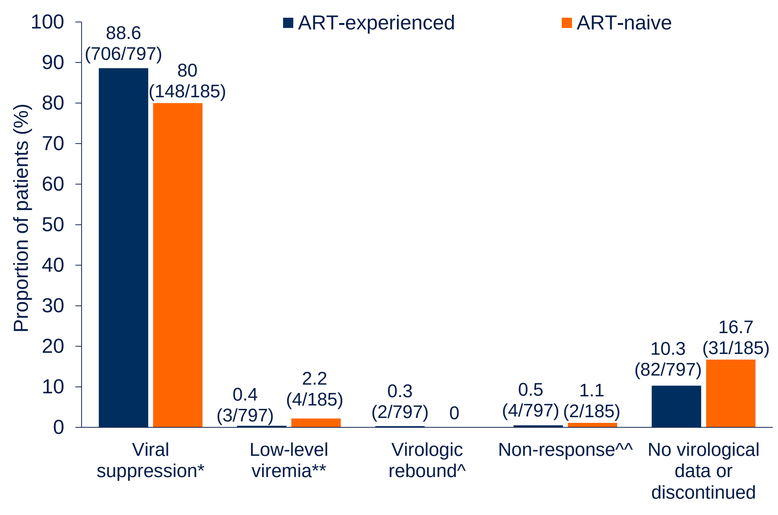
Safety

- By 12 months, 98 ADRs/SAEs were documented in 8.1% (80/982) of PLHIV, of which 56 ADRs in 54 PLHIV (5.5%) were evaluated as DTG-related. The 16 ADRs/SAEs in 13 PLHIV (1.3%) resulted in discontinuation or suspension of DTG.
- 43 SAEs were reported in 2.9% (n=28) PLHIV, 8 of which were fatal in 7 (0.7%) participants. All 7 deaths were not drug-related: acute left ventricular failure, cardiopulmonary failure, peritonitis, chemical poisoning, lung cancer metastatic, brain oedema and one cause was unknown. No serious ADR was reported.
- 47 ADRs/SAEs in 47 (4.8%) participants were grade 1, 21 ADRs/SAEs in 20 (2.0%) were grade 2, 21 ADRs/SAEs in 12 (1.2%) were grade 3, and only 1 ADR/SAE was grade 4.
- Majority of DTG-related ADRs (n=51) were laboratory and instrumental findings – weight increase >5% in 47 (4.8%) and liver enzymes elevation in 2 (0.2%) cases. 5 CNS-related ADRs were reported in 4 (0.4%) individuals.
- 14 (3.4%) female PLHIV became pregnant (12 detected in the 1st trimester, one case each in the 2nd and 3rd trimesters). The pregnancy outcomes were normal delivery in 7 WLHIV, planned abortion in 3 cases and one case each of missed abortion, miscarriage, and spontaneous miscarriage. One outcome was unknown as the female individual withdrew from the study.
- There were small weight changes: median BMI increased by +0.3 kg/m^2 (−0.2, 1.1) in FAS, +0.3 kg/m^2 (0.0, 1.1) and +0.2 kg/m^2 (−0.3, 1.1) in 2DR and 3DR subpopulations, respectively. No discontinuations due to weight gain were reported.

Effectiveness

- Viral suppression rates are depicted in Figure 3 and Table 2.
- Notably, in 88.6% of ART-experienced PLHIV, HIV-1 RNA levels were <250 cp/mL and 80% of ART-naive individuals were virally suppressed at 12 months.
- 81.9% of ART-experienced and 74.6% of ART-naive individuals had HIV-1 RNA levels <50 cp/mL at 12 months.
- Non-response was observed in 6 (0.6%) PLHIV and virologic rebound was found in only 2 (0.2%) individuals.
- All 11 ART-naive PLHIV in the 2DR subgroup were virally suppressed at 12 months (both <250 cp/mL and <50 cp/mL). 93.8% and 89.5% of ART-experienced 2DR individuals had VL <250 cp/mL and <50 cp/mL, respectively.
- Overall median (IQR) CD4+ cell count increased by 80.0 cells/μL (−20, 188). Median increase was 205 cells/μL and 62.5 cells/μL in ART-naive and ART-experienced PLHIV, respectively.

Figure 3. Virological Outcomes at Month 12 (FAS)



N=982; n=115/982 with missing data.
*VL <250 cp/mL. **VL >250 and <500 cp/mL. ^Two consecutive measurements of VL ≥500 cp/mL after previously achieved suppression (<250 cp/mL). ^^Two consecutive measurements of VL ≥250 cp/mL after at least 6 months of treatment.

Table 2. Virological Outcomes at Month 12 by ART Regimen

	2DR (n=269)	3DR (n=708)
HIV-1 RNA <250 cp/mL, n (%)	253 (94.1%)	597 (84.3%)
HIV-1 RNA <50 cp/mL, n (%)	242 (90.0%)	545 (77.0%)
Low-level viremia, n (%)	2 (0.7%)	5 (0.7%)
Non-response, n (%)	2 (0.7%)	4 (0.6%)
Virologic rebound, n (%)	0	2 (0.3%)
No virological data or discontinued, n (%)	12 (4.5%)	100 (14.1%)

Conclusions

- The use of DTG-based 3-drug and 2-drug regimens in this real-world Russian TESLA cohort was associated with a high level of effectiveness and safety through 12 months.
- The rate of ADRs associated with DTG was 5.5%, no new safety signals identified.
- Small weight changes reported in 4.8% with no discontinuation due to weight gain.

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References: 1. ECDC/WHO. HIV/AIDS surveillance in Europe 2021 – 2020 data; 2021. **2.** Central Research Institute of Epidemiology, Rospotrebnadzor. HIV fact sheet in Russia on 31.12.2021. http://www.hivrussia.info/dannye-po-vich-infektsii-v-rossii/.

Presenting author: Sergey Kuznetsov; sergey.d.kuznetsov@gsk.com

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