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Effectiveness and Safety of Dolutegravir in Children and Adolescents Living With HIV in Europe and Thailand

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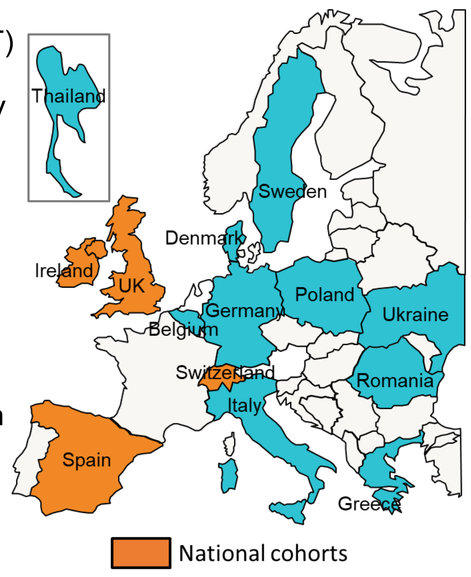
Background & Aim

Dolutegravir (DTG)-based antiretroviral therapy (ART) is the WHO-preferred first- and subsequent-line treatment for children and adolescents living with HIV (CALHIV).

Studies of CALHIV on DTG in **routine care** in sub-Saharan Africa have reported high levels of viral suppression (>80%) but there are limited safety data and follow up beyond 18 months.[1]

Aim: To assess **effectiveness and safety of DTG** in CALHIV in routine care across the European Pregnancy and Paediatric Infections Cohort Collaboration (**EPPICC**) network (Fig. 1).



1. Bacha et al. 2023. PIDJ 42(7) p576-581.

***Figure 1:** Location of EPPICC cohorts in DTG study.*

Methods

Inclusion criteria: CALHIV aged <18 years at start of DTG.

Effectiveness outcomes

- **Viral suppression:** proportion with viral load (VL) <50 copies/mL after 24, 48, 96, 144 and 192 (+/-12) weeks on DTG (analysed overall, by ART/VL status at DTG start, and by age group).

Safety outcomes

i. **Adverse events (AE):** frequency of AEs and serious AEs (SAEs) causally associated with DTG.

ii. **Laboratory abnormalities:** rates of DAIDS grade 1, 2, and ≥3 laboratory abnormalities.

iii. **Discontinuation:** cumulative incidence of discontinuation of DTG (all-cause) using Kaplan Meier methods and incidence of treatment-related (viral failure or toxicity) discontinuations estimated with other reasons for discontinuation treated as a competing risk.

Censoring: earliest of last visit, death, or discontinuation (censored at discontinuation date +30 days for safety outcomes). Data cut-off date: May 2023.

Results: Characteristics

***Table 1:** Demographic and clinical characteristics at DTG start (n=1231)*

		n (%), median [IQR]
Sex	Female	607 (50)
Age at ART initiation (years)		3 [1, 8]
Age at DTG start (years)		14 [11, 16]
	0-<6 years	70 (6)
	6-<12 years	319 (26)
	12-<18 years	842 (68)
Ethnicity	Black	520 (42)
	White	451 (37)
	Asian	130 (11)
	Other	105 (9)
Country/region	UK/Ireland	382 (31)
	Ukraine	282 (23)
	Spain	198 (16)
	Rest of Europe/Thailand	369 (30)
Perinatal acquisition		1020 (95)
ART/viral load status*	ART-naïve	120 (10)
	ART-exp/VL≥200c/mL	163 (13)
	ART-exp/VL<200c/mL	603 (49)
	ART-exp/unknown†	345 (28)
Median time on ART (years)‡		9 [5, 12]
CD4 cell count (cells/mm³)§		710 [492, 973]
Prior AIDS diagnosis¶		262 (21)

Percentages are calculated among those with complete data. 27 were missing sex, 25 missing ethnicity and 165 missing HIV acquisition route. * Closest within 12 weeks before and 1 week after DTG start. † 50% from Ukraine. ‡ ART-experienced only. § Closest within +/-12 weeks of DTG start. ¶ An additional 17 (1%) had an AIDS diagnosis but unknown if this was before DTG start.

Median **year of DTG start** was 2018 [IQR 2017, 2020].

Median **duration on DTG** was: 93 [49, 163] weeks.

Results: Effectiveness

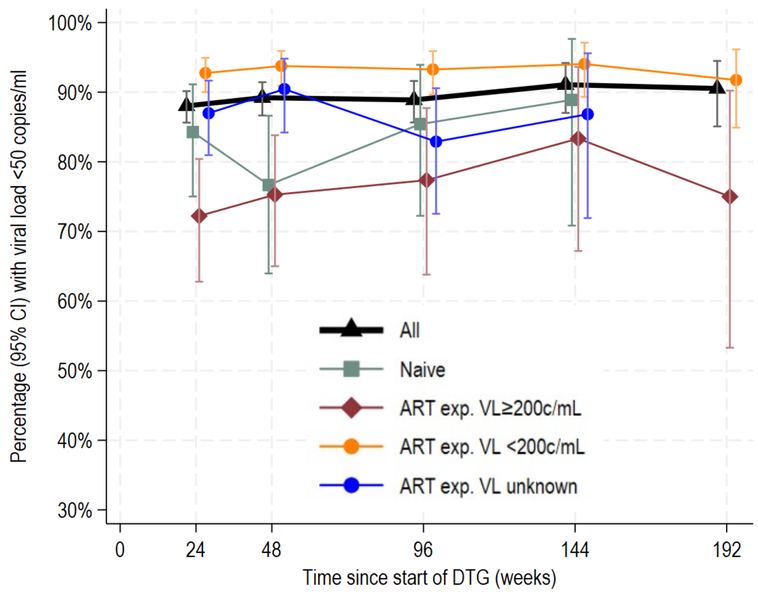


***Figure 2:** Viral suppression (<50 copies/mL) on a DTG-based regimen, overall and by ART and viral load status at DTG start.*

Overall, **88-91%** had suppressed VL over 4 years on DTG (Fig. 2).

Suppression was **highest** in CALHIV who were **ART-experienced and suppressed** at DTG start, and **lowest** in **ART-experienced and unsuppressed** at DTG start.

Population	n/N*	Viral suppression (<50 copies/mL) at 96 weeks
All	408/459	89% (95% CI 86, 92)
Naïve	41/48	85% (95% CI 72, 94)
ART exp. VL≥200c/mL	41/53	77% (95% CI 64, 88)
ART exp. VL<200c/mL	263/282	93% (95% CI 90, 96)
ART exp. VL unknown	63/76	83% (95% CI 73, 91)

* Patients in follow up, still on a DTG-based regimen with viral load data available at 96 (+/-12) weeks.

There were **no differences** in viral suppression **by age group** at DTG start (data not presented).

Results: Safety

- Table 2 summarises the total number of AEs, SAEs, DAIDS grade ≥3 lab events and all-cause discontinuation.
- **5 SAEs were causally associated with DTG** of which 4 led to discontinuation.
- There were **no deaths**.
- 848 (69%) CALHIV had laboratory data while on DTG, of whom **46 (5%) had 57 DAIDS grade ≥3 laboratory events**.

***Table 2:** Clinical AEs and SAEs with known causal relationship to DTG, grade ≥3 laboratory events, and discontinuation.*

Event	Patients with data	Patients with events, n (%)	Number of events	Details of events
All AEs causally related to DTG	1146	26 (2%)	52	5 SAEs in 5 patients (described below), 38 AEs in 13 patients, 9 AEs of unknown seriousness in 8 patients
SAEs causally related to DTG	1146	5 (0.4%) (4/5 discontinued DTG)	5	Headache, grade 3 raised creatinine, psychiatric disturbance, renal colic, and neurological event
DAIDS grade ≥3 lab events	848	46 (5%)	57	There were **≥5 events (patients)** for: LDL 5 (5), TRIG 6 (6), TBIL 7 (6), ANC 8 (8), Hb 11 (10)
All-cause discontinuation	1201	95 (8%) (discontinued at median 90 [IQR 36, 138] weeks)	95	Reasons: **viral failure 5 (5%); toxicity 17 (18%)**; treatment simplification 17 (18%); other/unknown 56 (59%)

AE, adverse event; ANC, absolute neutrophil count; DAIDS, Division of AIDS; DTG, dolutegravir; Hb, haemoglobin; IQR, interquartile range; LDL, low-density lipoprotein; SAE, serious adverse event, TBIL, total bilirubin; TRIG, triglycerides

- **Grade ≥3 laboratory event rates were <1 per 100 person-years (PY) for all markers** (Fig. 3).
- Grade 1 and 2 laboratory event rates were ≤15 events per 100 PY (highest among lipid markers).

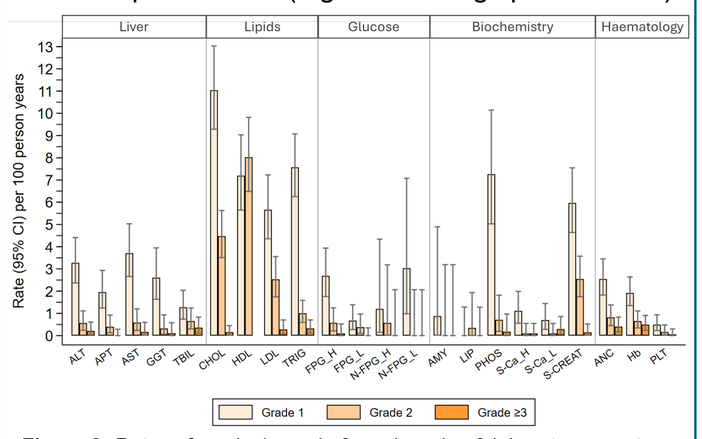


***Figure 3:** Rates of grade 1, grade 2, and grade ≥3 laboratory events while on a DTG-based regimen stratified by laboratory marker.*

ALT, alanine aminotransferase; AMY, amylase; ANC, absolute neutrophil count; APT, alkaline phosphatase; AST, aspartate aminotransferase; CHOL, total cholesterol; CI, confidence interval; FPG_H, high fasting blood glucose; FPG_L, low fasting blood glucose; GGT, gamma glutamyl transferase; Hb, haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein cholesterol; LIP, lipase; N-FPG_H, high non-fasting blood glucose; N-FPG_L, low non-fasting blood glucose; PHOS, serum phosphate; PLT, platelets; S-Ca_H, high serum calcium; S-Ca_L, low serum calcium; S-CREAT, serum creatinine; TBIL, total bilirubin; TRIG, triglycerides.

Cumulative incidence of discontinuation (95% CI):

All-cause discontinuation (Fig. 4)

- 5% (4, 7) by 96-weeks
- 10% (8, 12) by 144-weeks

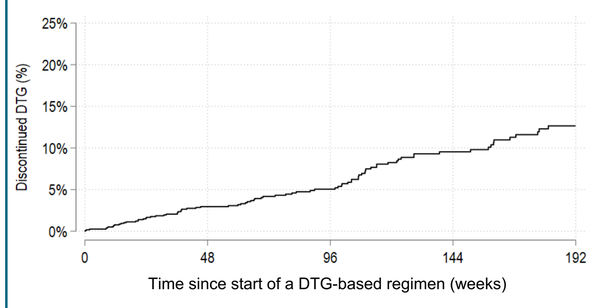


***Figure 4:** Cumulative incidence of all-cause discontinuation of DTG.*

Treatment-related discontinuation

- 1% (1, 2) by 96-weeks
- 2% (1, 3) by 144-weeks

Conclusions

Within this EPPICC cohort, at start of DTG **most** participants were **treatment-experienced adolescents**.

Overall **~90% were virally suppressed through 4 years on DTG,** however, lower proportions were virally suppressed among those who were treatment experienced and viremic at DTG start.

DTG was **generally well tolerated** with low numbers of SAEs causally related to DTG and few treatment-related discontinuations.

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