s.crichton@ucl.ac.uk

# Changes in body mass index before and after starting dolutegravir and compared to protease inhibitors in children and adolescents living with HIV in Europe and Thailand

Siobhan Crichton[1], Kate Edgar[1], Karen Scott[1], Elizabeth Chappell[1], Beatriz Álvarez[2], Luminita Ene[3], Luisa Galli[4], Tessa Goetghebuer[5], Cassidy Henegar[6], Thomas Ulrik Hoffmann[7], Christian Kahlert[8], Christoph Königs[9], Magdalena Marczyńska[10], Lars Naver[11,12], Talia Sainz[13], Wipaporn Natalie Songtaweesin[14], Vana Spoulou[15], Nattakarn Tantawarak[16], Vani Vannappagari[6], Alla Volokha[17], Anna Turkova[1], Ali Judd[1,18], Intira Jeannie Collins[1]
on behalf of the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC)

1 MRC Clinical Trials Unit at University College London, London, UK. 2 Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Infantil Vall d'Hebron, Barcelona, Spain. 3 "Dr. Victor Babes" Hospital for Infectious and Tropical Diseases, Bucharest, Romania. 4 Infectious Disease Unit, Meyer Children's Hospital, IRCCS; Department of Health Sciences, University of Florence, Florence, Italy. 5 Hopital St Pierre, Brussels, Belgium 6 Epidemiology and Real World Evidence, ViiV Healthcare, Durham, United States. 7 Department of Pediatrics, Hvidovre University Hospital, Copenhagen , Denmark. 8 Children's Hospital of Eastern Switzerland and Cantonal Hospital, Infectious Diseases and Hospital Epidemiology, St Gallen, Switzerland. 9 Goethe University, University Hospital Frankfurt, Department of Paediatrics and Adolescent Medicine, Frankfurt, Germany. 10 Department of Children's Infectious Diseases, Medical University of Warsaw, Warsaw, Poland. 11 Department of Pediatrics, Karolinska University Hospital, Stockholm, Sweden. 12 Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Stockholm, Sweden. 13 Hospital La Paz and La Paz Research Institute, Madrid, Spain. CIBERINFEC, Madrid, Spain. 14 Department of Pediatrics, and School of Global health, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand 15 First Dept of Paediatrics, "Agia Sofia" Children's Hospital, Athens, Greece 16 Khon Kaen University, Khon Kaen, Thailand 17 Shupyk National Healthcare, University of Ukraine, Kyiv, Ukraine. 18 Fondazione Penta ETS, Italy

## Introduction

Differences in weight changes on dolutegravir (DTG) compared to other regimens have been reported in some adult studies[1], but data in children and adolescents living with HIV (CALHIV) are limited.

**Aim: to describe changes in BMI before and after starting DTG and compared to protease inhibitors (PI)**

## Inclusion criteria

CALHIV followed in 15 observational cohorts in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC).

Analyses of **BMI before/after DTG start, and associated characteristics, included all CALHIV aged 2 to <18 years** at start of **any DTG containing regimen**.

**Comparative analyses of DTG and PI** included **CALHIV age 6 to <18 years at start of DTG or PI+2/3NRTI.**

## Methods

Mixed-models described changes in body mass index-for-age z-score (zBMI, UK 1990 growth reference).

- Changes in zBMI over time were modelled using linear splines, with placement of knots (i.e. points at which direction of the trajectory changes) selected based on 'best' model fit (using Akaike's Information Criteria, AIC) .
- All available zBMI measures within the timeframe of each analysis were used, with follow up censored at earliest of 96 weeks, last visit or 7 days after DTG/PI discontinuation.

First, **zBMI was estimated in the 48 weeks before and after DTG start** and characteristics (sex, age, ethnicity, pre-DTG regimen (categorised as containing tenofovir disoproxil fumarate (TDF) and/or efavirenz (EFV) (both shown to have weight lowering effects[2]) or not), NRTI backbone at start of DTG (tenofovir-alafenamide (TAF), TDF or neither), ART/viral load (VL) status and WHO immune status) associated with changes at start of DTG explored.

Second, multivariable models were used to identify **characteristics independently associated with zBMI up to 96 weeks** after DTG start. Variables with p<0.1 were included in the model.

Third, **zBMI changes over 96 weeks on DTG were compared to CALHIV starting PIs** (overall and by ART/VL status at DTG/PI start) using propensity scores to balance characteristics and weighted mixed models.

*NB analyses have been updated following submission of the abstract, but conclusions are unchanged*

## Results: Characteristics

Among 1231 CALHIV who started DTG, 948 had ≥1 zBMI in the first 96 weeks on DTG and were included

- Demographic and clinical characteristics at start of DTG are shown in Table 1 and 2
- Median [IQR] duration on DTG was 107 [64, 173] weeks

***Table 1:*** *Demographic characteristics*

| | Total (n=948) |
|---|---|
| **Female** | 471 (50%) |
| **Ethnicity** (n=925) | |
| Black | 442 (48%) |
| White | 300 (32%) |
| Asian | 103 (11%) |
| Other | 80 (9%) |
| **Country/region** | |
| UK/Ireland | 315 (33%) |
| Ukraine | 165 (17%) |
| Rest of Europe | 391 (41%) |
| Thailand | 77 (8%) |
| **Perinatal HIV** (n=833) | 796 (96%) |

***Table 2:*** *Characteristics at DTG start*

| | Total (n=948) |
|---|---|
| **Duration on ART** (years) | 9 [5, 12] |
| **zBMI** (n=780) | 0.3 [-0.6, 1.2] |
| **Prior AIDS** (n=938) | 194 (21%) |
| **ART & VL status** | |
| ART-naïve | 99 (10%) |
| ART-exp/VL ≥200c/mL | 124 (13%) |
| ART-exp/VL <200c/mL | 488 (52%) |
| ART-exp/unknown VL | 237 (25%) |
| **Regimen** | |
| Contained TAF | 67 (7%) |
| Contained TDF | 190 (20%) |
| No TDF/TAF | 691 (73%) |

## Results: zBMI before and after DTG start

741 CALHIV had ≥1 zBMI measurement 48 weeks before, and ≥1 measurement 48 weeks after DTG start.

In the **48 weeks before starting DTG zBMI increased by 0.07** (95% CI 0.03 to 0.11) and in the 48 weeks after DTG start by 0.13 (0.09 to 0.16) (p=0.087).

The **change in zBMI trajectory after starting DTG differed by regimen** (p=0.006) (Fig 1).

- Among those **not on TDF or EFV pre DTG**, z-scores **increased at a similar rate pre and post** DTG start.
- The **biggest change** in trajectory was observed in those **switching from TDF or EFV to TAF+DTG.**

Degree of change in the zBMI trajectory at start of DTG also **differed by age at DTG start** (p=0.006) **with 6 to <12-year-olds growing more rapidly after DTG start** than before.

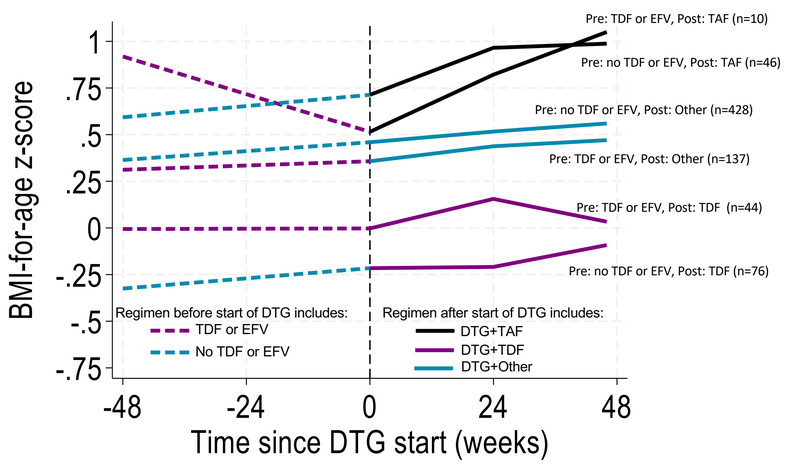



***Figure 1:*** *Mean zBMI before and after DTG start by regimen*

## Results: zBMI over 96 weeks on DTG v PI

***Table 3:*** *Characteristics at DTG/PI start of CALHIV included in propensity score analysis*

| | PI (n=368) | | DTG (n=543) |
|---|---|---|---|
| | Unweighted | Weighted | |
| | mean ± SD or % | | |
| **Male sex** | 46% | 42% | 48% |
| **Black ethnicity** | 70% | 54% | 58% |
| **Age at regimen start (years)** | 13.0±3.1 | 13.0 | 13.1±3.1 |
| **Prior AIDS diagnosis** | 19% | 18% | 22% |
| **Previously failed treatment** | 28% | 15% | 16% |
| **Time since ART initiation (years)** | 5.8±5.4 | 7.2 | 7.3±5.0 |
| **On TDF** | 38% | 11% | 10% |
| **ART naive** | 35% | 13% | 14% |
| **ART exp., VL≥200 copies/mL** | 27% | 16% | 15% |
| **ART exp., VL<200 copies/mL** | 38% | 71% | 71% |
| **BMI-for-age z-score** | 0.4±1.2 | 0.3 | 0.5±1.3 |

Propensity scores were derived separately by ART/VL group. All characteristics shown above were included in models apart from zBMI and for those naïve, prior treatment failure and time on ART. zBMI at regimen start was unknown for 13% of CALHIV. In sensitivity analyses in the subgroup with zBMI available, findings were unchanged when zBMI was additionally adjusted for.

In propensity scoring analysis, 543 CALHIV on DTG were compared to 368 on PIs.

CALHIV on PIs were **weighted to minimise differences in characteristics** between those on DTG and PIs (Table 3).

After propensity score weighting there **were no statistical differences in mean zBMI change over 96 weeks on DTG and PI-based regimen (Fig 3).**

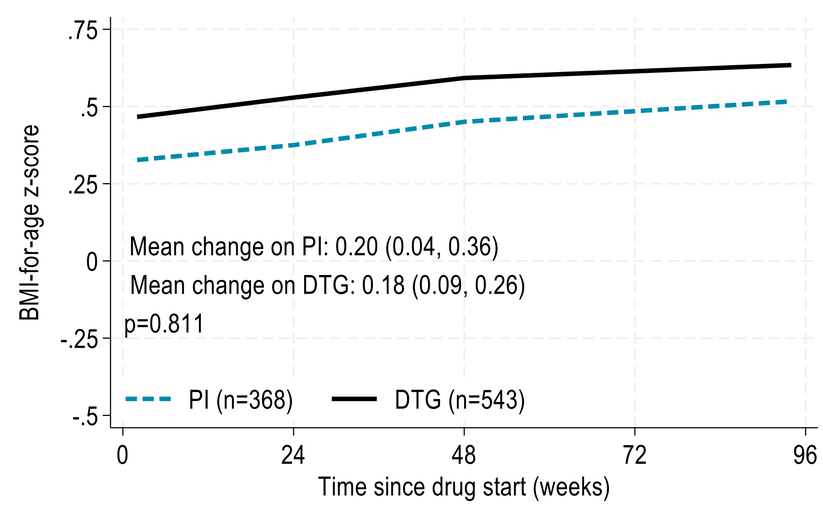
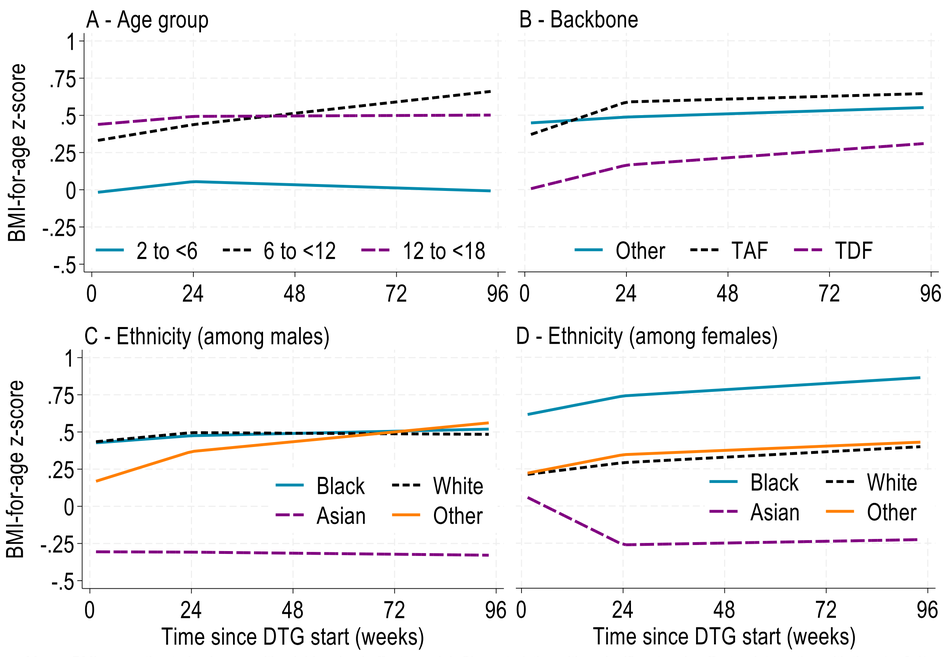



***Figure 3:*** *Mean zBMI over 96 weeks on DTG and PIs after propensity score weighting*

## Results: Characteristics associated with zBMI over 96 weeks on DTG




Mean zBMI was estimated using a multivariable mixed effects model. Characteristics with a significant main effect or interaction with time (p<0.1) were included in the model. The final model included region as a main effect, in addition to interactions between age and time, backbone and time, and a three-way interaction between sex, ethnicity and time.

***Figure 2:*** *Mean zBMI on DTG by age, backbone, sex and ethnicity*

Among all 948 CALHIV with ≥1 zBMI measures within 96 weeks of DTG start, **zBMI increased most rapidly in the first 24 weeks** on DTG (mean change=0.08 (0.04,0.12)), **then slowed** to a rate of 0.05 (0.01,0.09) per 48 weeks.

In multivariable analyses, **zBMI trajectories differed** by:

- **age** (p=0.002), with the largest increases in those age 6 to <12 years (Fig 2A),
- **backbone** (p=0.031), with the largest increases seen on TAF (Fig 2B), and
- **sex and ethnicity** (interaction p=0.090); the largest increase in males of other ethnicity (Fig 2C) and black females (Fig 2D).

ART/VL status and prior regimen (TDF or EFV containing versus other) were not significantly associated with zBMI change on DTG.

## Summary

**zBMI increases after starting DTG were similar to increases after starting PI. After DTG start, the largest gains were in children aged 6-<12 years at DTG start, in black females and those on DTG+ TAF; similar results have been found in adults[1].**

1 Kanters S, et al. EClinicalMedicine. 2022 May 12;48:101412. 2 Capeau, J et al.. Current Opinion in HIV and AIDS 19(1):p 14-20, January 2024

## Acknowledgements

**Cohorts participating in EPPICC and included in this study (PI):** Hospital St Pierre Cohort, Brussels, Belgium (T Goetghebuer); Denmark Copenhagen Cohort, Denmark (T Hoffman); German Pediatric and Adolescent HIV Cohort, Germany (C Königs); Greece Cohort, Greece (V Spoulou); Anna Meyer Children's University Hospital, Florence, Italy (L Galli); Paediatric Cohort, Poland (M Marczynska); "Victor Babes" Hospital Cohort, Bucharest, Romania (L Ene); CoRISPE-cat, Catalonia, Spain (A Noguera Julian); CoRISPES, rest of Spain cohort, Spain (M Navarro), Karolinska University Hospital, Stockholm, Sweden (L Naver); Swiss Mother and Child HIV Cohort Study, Switzerland (C Kahlert); Chulalongkorn University, Thailand (T Puthanakit); Khon Kaen Hospital Cohort, Thailand (N Tantawarak); Paediatric HIV Cohort Study, Odessa, Ukraine (A Volokha, R Malyuta); Collaborative HIV Paediatric Study, UK and Ireland (A Judd).

**We thank all the patients, families and clinic staff who contribute to cohorts in EPPICC.**

**This study was funded by ViiV healthcare.**
**EPPICC is a collaborative study coordinated by the Penta Foundation (http://penta-id.org) and UCL.**
The MRC Clinical Trials Unit at UCL is supported by the Medical Research Council (programme number: MC_UU_00004/03). Other EPPICC activities received industry funding from Gilead Sciences during the time this work was carried out.

Smarter Studies
Global Impact
Better Health