Dolutegravir and Growth in Pediatric Populations With HIV-1: IMPAACT P1093 and IMPAACT 2019

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Introduction

- DTG plus 2 nucleoside reverse transcriptase inhibitors is the preferred first-line antiretroviral therapy (ART) regimen for infants, children, and adolescents aged ≥4 weeks and weighing ≥3 kg living with HIV-1[1-4]
- Weight gain has been linked with use of integrase strand transfer inhibitor– or DTG-based regimens in some clinical studies of adults living with HIV-1[5,6] and some observational studies of children and adolescents living with HIV-1[7,8]
- However, weight gain was not linked with use of DTG in a randomized clinical trial comparing DTG- (n=350) vs efavirenz- or protease inhibitor–based ART (n=357) in children and adolescents living with HIV-1,[9] but more data are needed
- Here, BMI-based growth parameters were assessed in pediatric participants through 48 weeks in the IMPAACT P1093 (P1093) and IMPAACT 2019 studies

Methods

- P1093 and IMPAACT 2019 are phase 1/2, multicenter, open-label, non-comparative studies of DTG-based ART
  - DTG was evaluated in combination regimens in infants, children, and adolescents living with HIV-1 aged 4 weeks to <18 years at enrollment in P1093
  - DTG/abacavir/lamivudine fixed-dose combination was evaluated in children living with HIV-1 aged 6 months to <12 years at enrollment in IMPAACT 2019
- Separate descriptive post hoc analyses were performed for each study
- Age- and sex-specific BMI-for-age *z* score (BAZ; standard deviation scores) were calculated per 2006 and 2007 World Health Organization (WHO) references[10]
- BAZ was summarized at each visit from baseline to Week 48 by sex at birth, enrollment age and weight bands, and baseline BAZ
- Proportions of participants aged ≥2 years with increased BAZ weight category from baseline through Week 48 were summarized
- In P1093 and IMPAACT 2019, adverse events (AEs) were assessed using the Division of AIDS grading tables.[11] In the post hoc analyses, all AEs reported in both studies were reviewed, and AEs across several MedDRA system organ classes considered to have potential impact on growth were identified. AEs suggestive of change in growth parameters were further evaluated

Results

Baseline Demographics and Clinical Characteristics

- 181 participants were included in P1093, and 57 participants were included in IMPAACT 2019 (Table)
  - In P1093 and IMPAACT 2019, respectively, 48% and 46% of participants were female, 68% and 65% identified as Black or African American, and 87% and 95% were ART-experienced
  - In P1093 and IMPAACT 2019, respectively, 49% and 53% of participants were from Africa, 10% and 0% were from Brazil, 13% and 30% were from Thailand, and 28% and 18% were from the United States

Table. Baseline Demographics and Clinical Characteristics by Enrollment Age Band

	P1093 (N=181)					IMPAACT 2019 (N=57)		
Parameter	**4 wk to <6 mo (N=25)**	**6 mo to <2 y (N=42)**	**2 to <6 y (N=53)**	**6 to <12 y (N=38)**	**12 to <18 y (N=23)**	**6 mo to <2 y (N=9)**	**2 to <6 y (N=19)**	**6 to <12 y (N=29)**
Sex assigned at birth, n (%)								
Female	12 (48)	25 (60)	21 (40)	10 (26)	18 (78)	5 (56)	9 (47)	12 (41)
Male	13 (52)	17 (40)	32 (60)	28 (74)	5 (22)	4 (44)	10 (53)	17 (59)
Race, n (%)								
Asian	3 (12)	4 (10)	9 (17)	6 (16)	3 (13)	3 (33)	3 (16)	12 (41)
Black or African American	20 (80)	33 (79)	36 (68)	22 (58)	12 (52)	5 (56)	16 (84)	16 (55)
White	0	2 (5)	3 (6)	3 (8)	7 (30)	1 (11)	0	1 (3)
Other races[a]	2 (8)	3 (7)	5 (9)	7 (18)	1 (4)	0	0	0
Ethnicity, n (%)								
Hispanic or Latino	2 (8)	5 (12)	14 (26)	10 (26)	6 (26)	0	0	3 (10)
Not Hispanic or Latino	23 (92)	37 (88)	34 (64)	19 (50)	16 (70)	9 (100)	19 (100)	25 (86)
Unknown	0	0	5 (9)	9 (24)	1 (4)	0	0	1 (3)
ART-experienced	18 (72)	32 (76)	47 (89)	38 (100)	23 (100)	6 (67)	19 (100)	29 (100)
ART-naive	7 (28)	10 (24)	6 (11)	0	0	3 (33)	0	0
BMI, median (range), kg/m^2	16.1 (13.2-18.8)	16.0 (12.1-22.0)	15.5 (10.8-19.2)	15.8 (13.9-25.9)	20.6 (15.8-39.3)	14.6 (13.2-18.9)	14.6 (13.1-17.4)	14.7 (11.7-21.6)
BAZ, mean (SD)	−0.6 (1.2)	−0.2 (1.7)	0.2 (1.1)	−0.1 (1.0)	0.6 (1.6)	−0.7 (1.7)	−0.5 (0.9)	−0.9 (1.1)

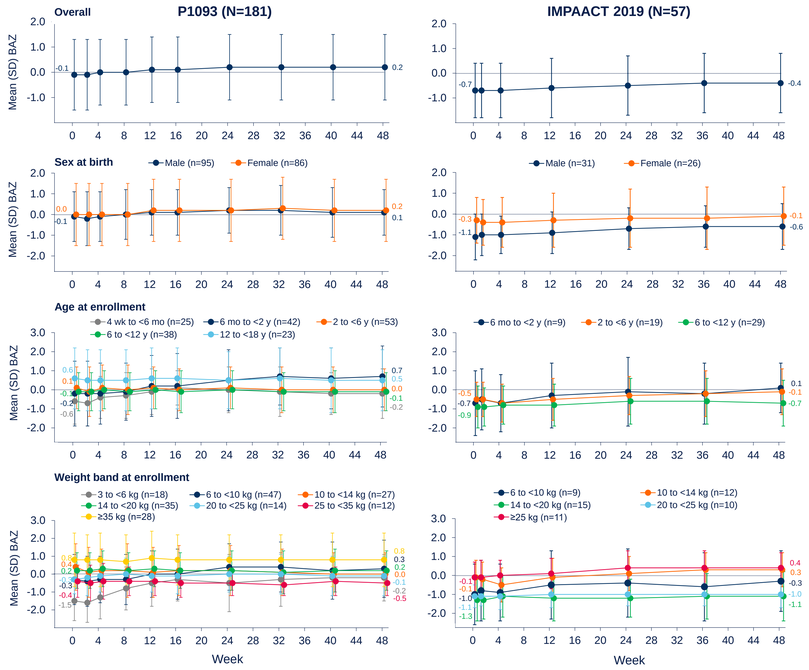
[a]Includes Native Hawaiian or Other Pacific Islander, individuals of other races, and individuals of unknown race.

Mean BAZ From Baseline Through Week 48

- Overall mean (SD) BAZ increased from −0.1 (1.4) at baseline to 0.2 (1.3) at Week 48 in P1093 and from −0.7 (1.1) to −0.4 (1.2) in IMPAACT 2019 (Figure 1)
  - There were generally small changes in mean BAZ between baseline and Week 48 in subgroups by sex (range, +0.2 to +0.5) and in subgroups by enrollment age bands (range, −0.1 to +0.9) across studies
  - Increases in mean BAZ >0.5 were observed in participants in the lowest weight (3 to <6 kg: P1093, +1.3 and 6 to <10 kg: P1093, +0.6; IMPAACT 2019, +0.7) and age bands (6 months to <2 years: P1093, +0.9; IMPAACT 2019, +0.8) at enrollment; BAZ was generally stable in other weight and age bands

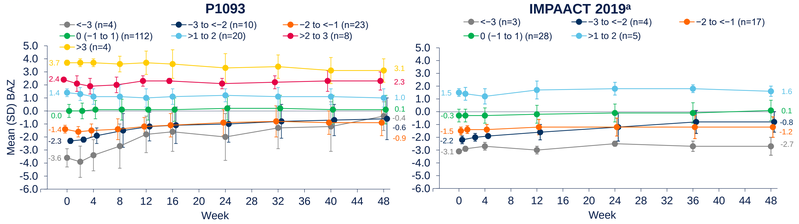
Children and adolescents initiating dolutegravir (DTG) had a small overall increase in mean body mass index (BMI)-for-age *z* score (BAZ) over 48 weeks; a more marked increase in mean BAZ was observed in some participants with BAZ <−2 at baseline, suggesting a return to health

Figure 1. Mean BAZ From Baseline to Week 48 Among Participants From P1093 and IMPAACT 2019 Overall and by Sex at Birth, Age at Enrollment, and Weight Band at Enrollment



Dotted line indicates BAZ of 0.

Figure 2. Mean BAZ From Baseline to Week 48 Among Participants From P1093 and IMPAACT 2019 by BAZ Category at Enrollment



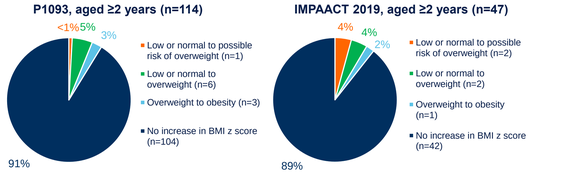
Dotted line indicates BAZ of 0. [a]Data are absent from weeks where no participants had data available.

- Improvements in BAZ were observed among participants with baseline BAZ <−3 and −3 to <−2 (Figure 2)

Increases in BAZ Weight Category Through Week 48 Across P1093 and IMPAACT 2019 Participants Aged ≥2 Years

- Among participants aged ≥2 years with low or normal BAZ weight category (≤1) at baseline, 5% (6/114) and 4% (2/47) shifted to the overweight BAZ weight category in P1093 and IMPAACT 2019, respectively; none developed obesity
- Among those with overweight BAZ weight category at baseline, 3% (3/114) and 2% (1/47) of P1093 and IMPAACT 2019 participants, respectively, had an increase in BAZ weight category to obesity at Week 48 (Figure 3)

Figure 3. Proportion of Participants Aged ≥2 Years at Enrollment From P1093 and IMPAACT 2019 With an Increase in BAZ Weight Category From Baseline to Week 48



WHO definitions for each BAZ category are presented in the table.

	WHO cutoffs for BAZ according to age[11,12]	
Category	**2 to ≤5 y**	**5 to ≤19 y**
Low or normal[a]	≤1	≤1
Possible risk of overweight	>1 to ≤2	NA
Overweight	>2 to ≤3	>1 to ≤2
Obesity	>3	>2

[a]Includes wasted, severe thinness, and thinness; there was no lower limit for BAZ.

AEs Suggestive of a Change in Growth Parameters Through Week 48

- In P1093, AEs suggestive of a change in growth parameters reported in ≥2% of participants were weight decrease (6% [10/181]), malnutrition (3% [5/181]), and failure to thrive (2% [4/181])
- In IMPAACT 2019, AEs suggestive of a change in growth parameters reported in ≥2% of participants were underweight (11% [6/57]) and malnutrition (4% [2/57])

Limitations

- BAZ was evaluated in this analysis; however, more data are needed to understand the consequences of BMI during infancy, and pediatric guidelines recommend using WHO weight-for-length, age-, and sex-specific charts from birth to 2 years of age[13]
- In the analysis of participants aged ≥2 years with increases in BAZ weight category, decreases in BAZ weight category through 48 weeks were not evaluated
- Excess weight gain is not included as an AE in the Division of AIDS grading table; thus, AEs do not reflect those of weight gain[10]
- In some subgroup analyses by BAZ category at enrollment, participant numbers were small

Conclusions

- In P1093 and IMPAACT 2019, the overall increase in mean BAZ was small 48 weeks after DTG initiation
- Across analyzed subgroups in both studies, mean BAZ was <1 at 48 weeks, equivalent to low or normal weight
- More marked increases in mean BAZ over 48 weeks were observed among some participants with the lowest BAZ (<−3 to <−2) at enrollment, suggesting a return to health
- Low proportions of participants aged ≥2 years at enrollment in P1093 (5%) and IMPAACT 2019 (4%) had an increase in BAZ weight category from low or normal BAZ (≤1) at baseline to overweight at Week 48

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References: 1. Panel on Antiretroviral Guidelines for Adults and Adolescents. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed January 18, 2024. **2.** Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf. Accessed January 18, 2024. **3.** World Health Organization. https://www.who.int/publications/i/item/9789240031593. Accessed January 18, 2024. **4.** European AIDS Clinical Society. https://www.eacsociety.org/media/guidelines-12.0.pdf. Accessed January 18, 2024. **5.** Sax et al. *Clin Infect Dis*. 2020;71:1379-1389. **6.** Venter et al. *Lancet HIV*. 2020;7:e666-e676. **7.** Thivalapill et al. *Clin Infect Dis*. 2021;73:e580-e586. **8.** Koay et al. *Open Forum Infect Dis*. 2021;8:ofab308. **9.** Turkova et al. *N Engl J Med*. 2021;385:2531-2543. **10.** Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrected v21.pdf. Accessed February 9, 2024. **11.** World Health Organization. https://www.who.int/toolkits/child-growth-standards/standards/body-mass-index-for-age-bmi-for-age. Accessed February 9, 2024. **12.** World Health Organization. https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age. Accessed February 9, 2024. **13.** Hampl et al. *Pediatrics*. 2023;151:e2022060640.

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