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Efficacy, Safety and Tolerability of Dispersible and Immediate Release Abacavir/Dolutegravir/Lamivudine Tablets in Children With HIV

IMPAACT 2019 Week 48 Results

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Background: Dispersible and immediate-release fixed-dose combinations (FDC) of abacavir, dolutegravir, and lamivudine are priority first-line antiretroviral therapy (ART) in children with HIV-1 (CWHIV). We report safety, efficacy and tolerability of these regimens through 48 weeks of treatment.

Methods: IMPAACT 2019 was a phase I/II, international, multisite, open-label, noncomparative study of dispersible and immediate-release FDC abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) in participants with HIV-1 <12 years of age weighing 6 to <40 kg. At entry, participants were ART-naive or ART-experienced and virally suppressed on stable ART for ≥6 months. Participants received weight-banded dosing and enrolled across 5 weight bands in parallel. Follow-up visits were completed at weeks 1, 4, 12, 24, 36 and 48.

Results: Fifty-seven participants were enrolled; 2 participants withdrew due to poor drug tolerability. Fifty-four of 55 participants on the study at week 48 remained on the study drug. All 54 participants who remained on study drug through week 48 had viral loads of <200 copies/mL. CD4-lymphocyte counts remained stable with age over 48 weeks. Mean change (95% confidence interval) in body mass index Z-scores was 0.4 (0.2–0.6). Nine study drug-related adverse events were reported. One drug-induced liver injury attributed to abacavir and dolutegravir led to the permanent discontinuation of the study drug.

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The data cannot be made publicly available due to the ethical restrictions in the study's informed consent documents and in the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network's approved human subjects protection plan; public availability may compromise participant confidentiality. However, data are available to all interested researchers upon request to the IMPAACT Statistical and Data Management Center's data access committee (email address: sdac.data@fstrf.org) with the agreement of the IMPAACT Network.

All members of the writing team reviewed the final manuscript. H.R., D.E.Y., K.B., I.M., A.C., P.F., L.Z., S.W. and Y.R. took responsibility for writing the manuscript. L.Z., Y.R. and L.Z. also performed data analysis. Other authors reviewed data and contributed to the manuscript.

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Conclusions: Dispersible FDC ABC/DTG/3TC is the first dispersible dolutegravir-containing single tablet regimen for CWHIV. Dispersible- and immediate-release ABC/DTG/3TC was observed to be generally safe, effective and well-tolerated in CWHIV through 48 weeks.

Key Words: pediatric, fixed-dose combination, antiretroviral, integrase inhibitor, nucleoside reverse transcriptase inhibitors

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Globally, 1.4–1.7 million children are living with HIV-1 (CWHIV), predominantly in Eastern and Southern Africa.[1] Despite advances in prevention, approximately 120,000 children acquired HIV-1 (HIV) in 2023. Although effective antiretroviral therapy (ART) is available, only 57% of CWHIV are accessing ART.[1] In 2023, among CWHIV, 48% (39%–60%) had a suppressed viral load.[1] Poor outcomes can partially be attributed to delays in access to the most effective antiretrovirals and fixed-dose combinations (FDC), disproportionately affecting the youngest children.[2]

Dolutegravir, an integrase strand transferase inhibitor (INSTI), is safe and superior for first- and second-line treatment compared to nonnucleoside reverse transcriptase inhibitors or protease inhibitors as anchor drugs.[3,4] Dolutegravir can be used from 4 weeks of age and weight ≥3 kg.[4,5] Fifty-milligram immediate-release tablets can be used in children weighing ≥20 kg.[3,4] Dolutegravir with nucleoside reverse transcriptase inhibitors abacavir and lamivudine is a World Health Organization (WHO) recommended first-line regimen for CWHIV.[3] With increasing access to 5 mg (unscored) and 10 mg scored dispersible dolutegravir tablets, approximately 160,000 CWHIV were taking dolutegravir in 2023.[6]

Single-tablet, once-daily FDC options are associated with improved medication adherence and treatment outcomes in adults living with HIV.[7] Few FDCs are available for infants and CWHIV under 30 kg. A FDC dispersible formulation of abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) was identified as a priority by the Pediatric ARV Drug Optimization for HIV group.[2]

The pharmacokinetics, safety, tolerability and efficacy of dispersible and immediate-release ABC/DTG/3TC were evaluated in CWHIV in the IMPAACT 2019 study. Data through 24 weeks of therapy were published[8] and data through 48 weeks supported regulatory approvals of both formulations for children 3 months of age and older and weighing ≥6 kg by the United States Food and Drug Administration (FDA) in 2023 and the European Medicines Agency in 2024.[9,10] We now present safety, tolerability, efficacy and growth data through 48 weeks of therapy.

METHODS

IMPAACT 2019 was a phase I/II, multisite, open-label, noncomparative dose confirmation study conducted in Botswana, South Africa, Thailand and the United States. The primary objectives were to confirm the dosing of ABC/DTG/3TC and to evaluate the safety profile at 24 weeks of treatment.[8] Key secondary objectives were to evaluate safety, tolerability, virologic efficacy and immunologic response through 48 weeks of therapy. CWHIV <12 years and weighing 6 to <40 kg were eligible to enroll across 5 weight bands. Treatment-experienced children could enroll if they were on an ART regimen with HIV-1 RNA <200 copies/mL for ≥6 months before entry. Children receiving nonnucleoside reverse transcriptase inhibitors or rifamycin were excluded to avoid possible drug-drug interactions. Documented nucleoside reverse transcriptase inhibitors resistance with a known M184V resistance mutation was allowed. Those with HLA B*5701 genotype were excluded. All eligibility criteria, procedures, doses (Table 1) and follow-up were described previously.[8]

HIV-1 RNA viral load was collected at screening, entry and weeks 4, 12, 24, 36 and 48 with additional monitoring for children with a M184V resistance mutation at weeks 8, 16 and 20. Confirmed virologic failure was defined as 2 consecutive (within 28 days) plasma HIV-1 RNA viral loads ≥200 copies/mL ≥24 weeks after enrollment for ART-naive participants or at any time for ART-experienced participants. Participants with confirmed virologic failure were evaluated for viral resistance from stored specimens taken at baseline and time of virologic failure confirmation, deep sequencing was planned. Laboratory-based safety assessment was performed at screening and weeks 4, 12, 24, 38 and 48. Creatinine was determined using isotope dilution mass spectrometry-traceable methodology and the estimated glomerular filtration rate (eGFR) was calculated using the 2009 Schwartz Bedside Pediatric eGFR formula.[11] Nonfasting lipid profile was performed at screening and week 24 and 48. CD4 testing was performed at screening and weeks 4, 12, 24 and 48.

Tolerability and adherence were assessed with caregiver questionnaires at weeks 4, 12, 24 and 48, early study discontinuation, and virologic failure confirmation visits. Sleep and mood over the prior 30 days were assessed with questionnaires at entry and weeks 4 and 24.

Adverse events (AEs) were graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected version 2.1, July 2017). In a sensitivity analysis, AEs were summarized, excluding changes from baseline in eGFR and serum creatinine and included grading on actual values only.

All analyses were done on the all-treated population, defined as children who received at least 1 dose of the study drug. Analyses were performed by weight band at enrollment and used a while-on-treatment strategy (ie, participants were right-censored the day after treatment discontinuation). Virologic response was summarized by the proportion of participants with viral suppression of less than 200 and 50 copies/mL and the FDA snapshot algorithm. The probability of experiencing a safety event and of having a successful virologic response based on the FDA snapshot algorithm were estimated with 95% exact confidence intervals (95% CIs). Height, weight and body mass index (BMI) were summarized, and height/length-for-age Z-score (HAZ), weight-for-age Z-score (WAZ) and BMI-for-age Z-scores (BAZ) were calculated based on WHO standards.[12] WAZ were only provided for children <10 years old at the time of measurement. SAS Version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

The protocol was approved by DAIDS, National Institute of Allergy and Infectious Diseases, United States National Institutes of Health; a single institutional review board for sites in the United States; and local institutional review boards for sites outside the United States. The study was registered on ClinicalTrials.gov (NCT 03760458). Written informed consent was obtained from participants' parent or legal guardians; assent was obtained where applicable in accordance with local requirements. After IMPAACT 2019 concluded, children without access to the study drug were eligible to enroll in a subsequent trial for continued access (NCT03016533).

RESULTS

From September 2020 to June 2021, 57 participants from ages 1 to 11 years enrolled; 28 (49%) were 1–<6 years of age. Three participants were ART-naive at enrollment. Weight ranged from 8.2 to 39.3 kg (Table 1).[8]

Fifty-five participants remained on study and 54 on study drug through week 48 (Table 1). Two (1 each from 6 to <10 kg and 10 to <14 kg weight bands, taking dispersible ABC/DTG/3TC)

TABLE 1. Summary of Baseline Information

Weight Band (kg)	6 to <10	10 to <14	14 to <20	20 to <25	≥25	Total
Tablets and Dosing	3 DT	4 DT	5 DT	6 DT	1 IR	
(ABC/DTG/3TC) mg	(180/15/90)	(240/20/120)	(300/25/150)	(360/30/180)	(600/50/300)	
Number Enrolled	n = 9	n = 12	n = 15	n = 10	n = 11	n = 57
Age (years)						
Median (Q1, Q3)	1.4 (1.1, 1.9)	3.6 (2.2, 3.7)	6.4 (4.7, 7.5)	8.4 (7.8, 8.9)	9.7 (9.5, 10.5)	6.4 (3.5, 8.8)
<6 years	9 (100%)	12 (100%)	7 (47%)	0 (0%)	0 (0%)	28 (49%)
Weight (kg)						
n	9	12	15	10	11	57
Median (Q1, Q3)	9.2 (8.5, 9.5)	12.9 (12.5, 13.7)	17.0 (15.9, 18.8)	21.5 (21.0, 23.3)	28.5 (26.0, 35.6)	17.0 (12.8, 22.1)
Minimum, maximum	8.2, 9.6	10.3, 13.8	14.4, 19.6	20.0, 24.6	25.6, 39.3	8.2, 39.3
Female sex	5 (56%)	7 (58%)	5 (33%)	3 (30%)	6 (55%)	26 (46%)
Antiretroviral (ART) experience						
ART-experienced n (%)	6 (67%)	12 (100%)	15 (100%)	10 (100%)	11 (100%)	54 (95%)
ART-naive n (%)	3 (33%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (5%)
HIV RNA Viral Load <200 copies/mL* n (%)	5 (56%)	12 (100%)	15 (100%)	10 (100%)	11 (100%)	53 (93%)
ART-experienced n (%)	5 (83%)	12 (100%)	15 (100%)	10 (100%)	11 (100%)	53 (98%)
ART-naive n (%)	0 (0%)	-	–	–	–	0 (0%)
M184V mutation n (%)	0 (0%)	0 (0%)	2 (13%)	0 (0%)	2 (18%)	4 (7%)
WHO weight-for-age Z-score†						
n	9	12	15	10	7	53
Median (Q1, Q3)	−1.1 (−1.6, −0.7)	−1.0 (−1.3, 0.1)	−1.1 (−2.7, −0.5)	−1.0 (−1.8, −0.9)	−0.3 (−0.8, 1.3)	−1.0 (−1.5, −0.3)
Mean (SD)	−1.2 (0.9)	−0.8 (1.0)	−1.4 (1.1)	−1.2 (0.7)	0.0 (0.9)	−1.0 (1.0)
WHO height-for-age Z-score						
n	9	12	15	10	11	57
Median (Q1, Q3)	−0.5 (−2.0, 0.2)	−1.1 (−1.6, −0.4)	−1.2 (−1.3, −0.3)	−0.8 (−1.1, −0.3)	−0.5 (−1.2, −0.3)	−0.8 (−1.3, −0.3)
Mean (SD)	−0.8 (1.7)	−1.1 (1.1)	−0.8 (1.2)	−0.7 (0.7)	−0.5 (1.2)	−0.8 (1.2)
WHO BMI-for-age Z-score						
n	9	12	15	10	11	57
Median (Q1, Q3)	−1.7 (−1.8, −0.6)	−0.3 (−0.8, 0.7)	−1.2 (−2.0, −0.3)	−1.0 (−1.5, −0.7)	−0.3 (−0.6, 0.3)	−0.7 (−1.5, −0.1)
Mean (SD)	−1.0 (1.6)	−0.1 (0.9)	−1.3 (1.1)	−1.1 (0.6)	−0.1 (0.8)	−0.7 (1.1)
WHO stage n (%)						
Stage 1	8 (89%)	8 (67%)	12 (80%)	8 (80%)	7 (64%)	43 (75%)
Stage 2	0 (0%)	1 (8%)	0 (0%)	0 (0%)	1 (9%)	2 (4%)
Stage 3	1 (11%)	1 (8%)	3 (20%)	1 (10%)	3 (27%)	9 (16%)
Stage 4	0 (0%)	2 (17%)	0 (0%)	1 (10%)	0 (0%)	3 (5%)

*Among ART-naive, viral loads were 186,419, 500,885 and 3,519,602 copies/mL at baseline. ART-experienced participants were eligible for the study if virologically suppressed (<200 copies/mL) for at least 6 months.

†Weight-for-age Z-scores were calculated for children 10 years or younger.

DT indicates dispersible tablet; IR, immediate release; WHO, World Health Organization.

withdrew from the study within 8 days of enrollment due to study drug palatability problems. A third child, taking the immediate-release tablet, had a 3-week interruption of study drug due to relocation before week 24 but subsequently returned to the study. At week 36, 1 participant permanently discontinued ABC/DTG/3TC due to drug-induced liver injury (DILI).

Twenty-seven participants increased study drug dosing due to growing into higher weight bands, including 7 who transitioned from dispersible to immediate-release tablets.

Virologic and Immunologic Response

At week 48, all 54 participants (100%) who remained on study drug at week 48 had HIV-1 RNA viral loads <200 copies/mL, and 45 (83%) had HIV-1 RNA viral loads ≤50 copies/mL, including 2 of 3 treatment-naive participants (see Table, Supplemental Digital Content 1, https://links.lww.com/INF/G240). Over 48 weeks, 1 (1.8%) participant met the study definition of virologic failure while taking the study drug.[8] This participant was ART-naive, remained on study drug, and had a viral load of 76 copies/mL at week 48. The 4 participants with a known M184V resistance mutation at enrollment maintained viral loads <200 copies/mL through 48 weeks. Overall, 54 of 57 [94.7%, 95% CI: (85.4–98.9)] participants had virologic success of <200 copies/mL based on the FDA snapshot algorithm.

CD4 cell count and percentage remained stable according to age-appropriate norms from baseline over 48 weeks (see Table, Supplemental Digital Content 2, https://links.lww.com/INF/G240).[13] Mean (SD) CD4 percentage was 35 (7.6%) across weight bands at Week 48.

Growth

Baseline mean (SD) HAZ, WAZ and BAZ were −0.8 (1.2), −1.0 (1.0) and −0.7 (1.1), respectively (Table 1). Over 48 weeks, the mean (95% CI) change in HAZ was −0.1 (−0.2–0.1), whereas the mean change in WAZ was 0.2 (0.1–0.4). At week 48, mean (95% CI) HAZ and WAZ were each −0.9 (−1.2, −0.6). Mean (95% CI) BMI at baseline was 15.0 (14.5–15.4) kg/m^2 and BMI Z-score −0.7 (−1.1, −0.4), mean change in BMI Z-score was 0.4 (0.2–0.6) (Fig. 1A–C).

Safety

No deaths occurred. Fifteen participants (26.3%, 95% CI: 15.5–39.7%) (Table 2) had at least 1 AE related to the study drug.

One AE led to the permanent discontinuation of the study drug. A 7-year-old treatment-experienced male from Thailand receiving ABC/DTG/3TC dispersible FDC (360/30/180 mg) experienced hepatitis at week 36, leading to ART interruption. The event

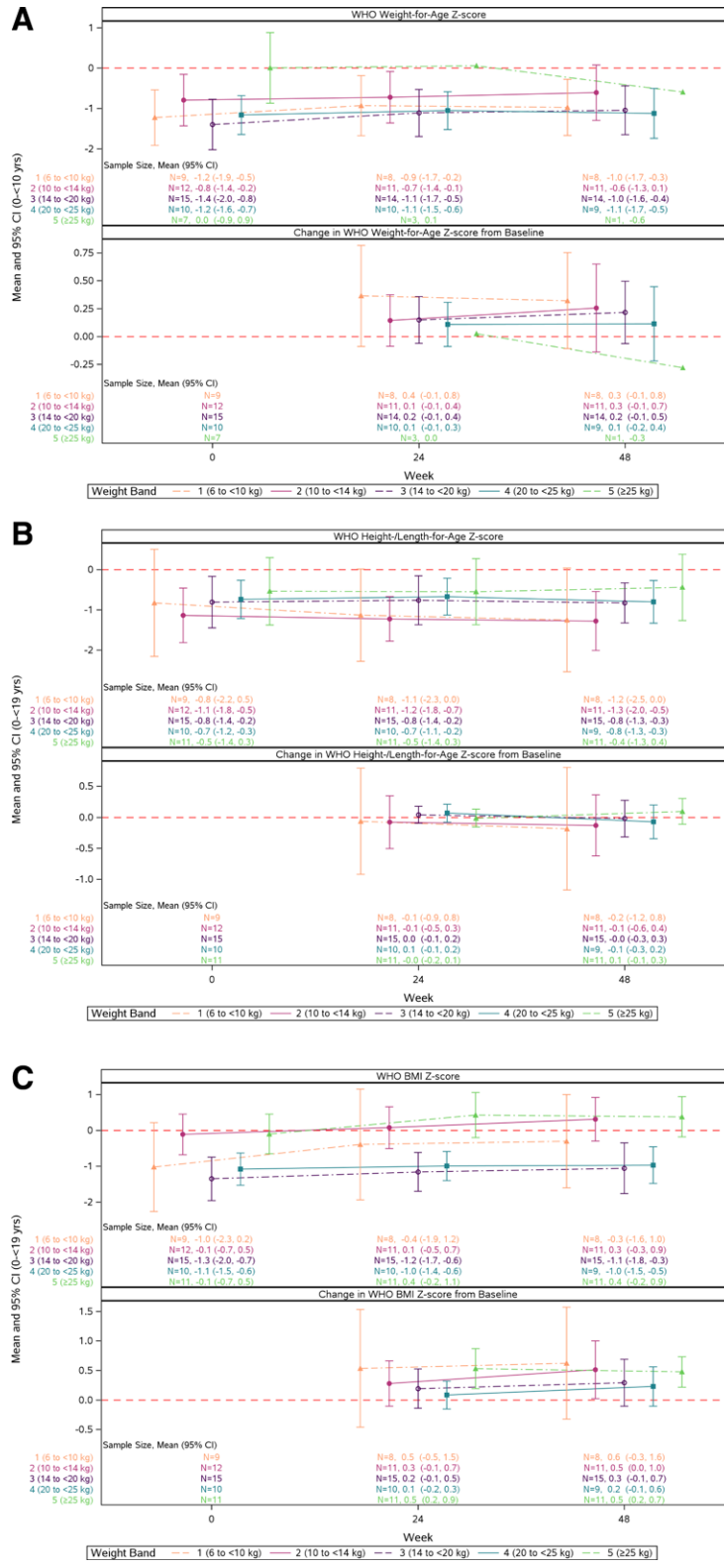

FIGURE 1. A: Mean and 95% confidence interval of World Health Organization weight for age Z-score for children younger than 10 years at baseline, week 24 and week 48 and change from baseline at week 24 and week 48. B: Mean and 95% confidence interval of World Health Organization length/height Z-score for children younger than 10 years at baseline, week 24 and week 48 and change from baseline at week 24 and week 48. C: Mean and 95% confidence interval of World Health Organization body mass index Z-score for children younger than 19 years at baseline, week 24 and week 48 and change from baseline at week 24 and week 48.

TABLE 2. Adverse Events Through Week 48 by Weight Band

Adverse Event Based on DAIDS Grading Table	6 to <10 kg (N = 9)		10 to <14 kg (N = 12)		14 to <20 kg (N = 15)		20 to <25 kg (N = 10)		≥25 kg (N = 11)		Total (N = 57)	
	n (%)	95% CI‡	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any adverse event	8 (88.9)	51.8–99.7	10 (83.3)	51.6–97.9	15 (100.0)	78.2–100.0	10 (100.0)	69.2–100.0	10 (90.9)	58.7–99.8	53 (93.0)	83.0–98.1
Adverse event assessed as related to study drug*	4 (44.4)	13.7–78.8	2 (16.7)	2.1–48.4	1 (6.7)	0.2–31.9	4 (40.0)	12.2–73.8	4 (36.4)	10.9–69.2	15 (26.3)	15.5–39.7
Grade 3 or higher adverse event	3 (33.3)	7.5–70.1	4 (33.3)	9.9–65.1	5 (33.3)	11.8–61.6	3 (30.0)	6.7–65.2	0	0.0–28.5	15 (26.3)	15.5–39.7
Grade 3 or grade 4 adverse event assessed as related to study drug*	0	0.0–33.6	0	0.0–26.5	0	0.0–21.8	2 (20.0)	2.5–55.6	0	0.0–28.5	2 (3.5)	0.4–12.1
Grade 5 adverse event assessed as related to study drug*	0	0.0–33.6	0	0.0–26.5	0	0.0–21.8	0	0.0–30.8	0	0.0–28.5	0	0.0–6.3
Serious† adverse event (per ICH criteria) assessed as related to study drug*	0	0.0–33.6	0	0.0–26.5	0	0.0–21.8	1 (10.0)	0.3–44.5	0	0.0–28.5	1 (1.8)	<0.1–9.4
Life-threatening adverse event assessed as related to study drug*	0	0.0–33.6	0	0.0–26.5	0	0.0–21.8	0	0.0–30.8	0	0.0–28.5	0	0.0–6.3
Adverse event assessed as related to study drug* that led to permanent discontinuation of study drug	0	0.0–33.6	0	0.0–26.5	0	0.0–21.8	1 (10.0)	0.3–44.5	0	0.0–28.5	1 (1.8)	<0.1–9.4

*Drug-relatedness of adverse events was determined by the site.
†Serious adverse events were defined according to Version 2.0 of the DAIDS EAE Manual.
‡95% CI = exact 95% confidence interval (Clopper-Pearson).

was categorized as a grade 4 DILI attributed to abacavir and dolutegravir. After a thorough investigation no other cause was found. Study drug was permanently discontinued, and he resumed his prior ART regimen once the DILI improved. His drug exposures for ABC, DTG and 3TC at week 1 and sparse drug concentrations at weeks 4, 12, 24 and 36 were comparable to other participants receiving the same dose.

One child had a grade 3 change in eGFR, and blood creatinine attributed to the study drug at week 39. This participant received 6 ABC/DTG/3TC dispersible tablets (ie, 360/30/180 mg) for 26 weeks and switched to the immediate-release tablet thereafter. Dosing was weight-appropriate. Serum creatinine results and eGFR were within normal limits for age at the local laboratory. After discussion with the study clinical management committee, this participant remained on ABC/DTG/3TC immediate-release tablets.

Increases in blood creatinine and decreases in eGFR from baseline values were common, occurring in 26 (45.6%) and 36 (63.2%) participants, respectively, while taking the study drug. Seven (12.3%) and 5 (8.8%) experienced a grade 3 or higher event for increased eGFR and blood creatinine compared to baseline, respectively. When grading using only actual values of eGFR and blood creatinine (rather than change from baseline), no participants experienced a grade 3 or higher event for eGFR or creatinine (Table 3).

Six (10.5%) participants experienced at least 1 nervous system disorder event (all grade 1 events), including headache (n = 3, 5.3%), somnolence (n = 2, 3.5%), dizziness (n = 1, 1.8%) and lethargy (n = 1, 1.8%). Sleep and mood questionnaires at week 24 were available from 55 participants' caregivers (see Table, Supplemental Digital Content 3, https://links.lww.com/INF/G240 and Table, Supplemental Digital Content 4, https://links.lww.com/INF/G240). Feelings of self-harm were noted in 1 participant at baseline only and 1 participant expressed new thoughts that life was not worth living at week 4. Four of 29 (14%) participants 6 years or older had difficulty with concentration at baseline and 1 (3.4%) at week 24. This was not reported for any participants younger than 6 years. At baseline, 10 (18%) participants took more than 30 minutes to fall asleep compared to 7 (13%) at week 24. The frequency of nightmares increased from study entry. At week 24, 3 (5.5%) participants experienced nightmares more than 3 times a week and 2 (3.6%) experienced nightmares once or twice a week. Four of these 5 participants had no or infrequent nightmares prior to study entry. One participant had grade 2 nightmares related to the study drug.

Nonfasting total cholesterol, low-density lipoprotein, high-density lipoprotein and triglycerides generally declined over 48 weeks (see Table, Supplemental Digital Content 2, https://links.lww.com/INF/G240).

Tolerability

Information gathered from acceptability and palatability questionnaires was available from 54 caregivers at week 48. Two participants discontinued within the first week due to poor palatability. Both consistently spit up medication, with 1 caregiver indicating that the participant needed to be held and continually refused treatment. Except 1, all participants receiving the immediate-release tablet took it whole. Most caregivers reported that the dispersible tablet took less than 3 minutes to dissolve [33 of 38 (87%)]. Sixty-seven percent of participants in the 14 to <25 kg weight bands took dispersed medication easily and by themselves. All participants in the 6 to <10 kg weight band took medication easily with help. The largest variation occurred in participants in the 10 to <14 kg weight band (median age 3.6 years at enrollment): 4 participants (36%) took medication easily

TABLE 3. Laboratory-based Adverse Events Through Week 48 for All Weight Bands

Grade	1	2	3	4	5	1–5
Laboratory Adverse Events per DAIDS Grading (N = 57)						
Glomerular filtration rate	Not applicable	29 (50.9%)	6 (10.5%)	1 (1.8%)	0	36 (63.2%)
Blood creatinine increased	4 (7.0%)	17 (29.8%)	4 (7.0%)	1 (1.8%)	0	26 (45.6%)
Alanine aminotransferase increased	18 (31.6%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	0	21 (36.8%)
Aspartate aminotransferase increased	12 (21.1%)	0	1 (1.8%)	0	0	13 (22.8%)
Blood cholesterol increased	6 (10.5%)	3 (5.3%)	0	0	0	9 (15.8%)
Low-density lipoprotein increased	2 (3.5%)	3 (5.3%)	0	0	0	5 (8.8%)
Hemoglobin decreased	4 (7.0%)	0	0	0	0	4 (7.0%)
Neutrophil count decreased	1 (1.8%)	3 (5.3%)	0	0	0	4 (7.0%)
Blood bilirubin increased	2 (3.5%)	1 (1.8%)	0	0	0	3 (5.3%)
Creatinine renal clearance decreased	0	2 (3.5%)	1 (1.8%)	0	0	3 (5.3%)
Blood alkaline phosphatase increased	1 (1.8%)	0	0	0	0	1 (1.8%)
Blood triglycerides increased	1 (1.8%)	0	0	0	0	1 (1.8%)
Gamma-glutamyltransferase increased	1 (1.8%)	0	0	0	0	1 (1.8%)
Platelet count decreased	1 (1.8%)	0	0	0	0	1 (1.8%)
Sensitivity analysis* of glomerular filtration and blood creatinine laboratory tests (N = 56)†						
Glomerular filtration rate based on actual values, only	Not applicable	11 (19.6%)	0	0	0	11 (19.6%)
Blood creatinine based on actual values, only	7 (12.5%)	1 (1.8%)	0	0	0	8 (14.3%)

*In the sensitivity analysis, serum creatinine and eGFR actual value grading was based on actual values alone per the DAIDS grading table, but did not include changes from baseline.

†Counts and proportions were calculated from a total of 56 participants. These included participants with an available eGFR or creatinine laboratory test.

by themselves; 5 (46%) took treatment easily with help; 1 (9%) needed to be promised a reward or threatened with punishment, and 1 (9%) needed to be held and forced to take treatment. Comparing the responses of participants to medication to when eating their favorite food, responses to taking the study drug were worse. Across study weeks, caregivers reported 11%–13% of participants having a bad or very bad facial reaction to taking study treatment (see Table, Supplemental Digital Content 5, https://links.lww.com/INF/G240).

DISCUSSION

Dispersible ABC/DTG/3TC is the first dispersible dolutegravir-containing single-tablet regimen for CWHIV. The FDC dispersible tablet and immediate-release tablets were observed to be effective and safe over 48 weeks.

There was no observed viral rebound (≥200 copies/mL) in the 4 participants with documented M184V resistance mutation, but all were virally suppressed at entry. One ART-naive participant did not achieve a viral load of <200 copies by 24 weeks, but demonstrated consistent viral load decrease, and achieved a viral load <200 copies/mL by week 36. Slower suppression is well documented in younger CWHIV starting therapy with high viral loads, as in this case.[14] At week 48, 9 of 154 naive children enrolled into the dolutegravir arm of the ODYSSEY study experience failure, but the number of naive children in IMPAACT 2019 is too small for appropriate comparison.[4]

ABC/DTG/3TC was generally safe and well-tolerated. Two participants discontinued the study drug due to palatability issues. One participant permanently discontinued the study drug due to DILI. The participant with DILI appeared to tolerate the study drug through week 36 but then developed DILI. Several possible mechanisms of DILI include liver cell stress, mitochondrial toxicity, hypersensitivity, steatosis and immune reconstitution.[15] Abacavir-related hepatotoxicity is rare and occurs almost exclusively in persons with HLA B*5701 genotype. All participants in this study were HLA B*5701 genotype negative.[16] Dolutegravir discontinuation due to hepatitis was reported in fewer than 2 percent of adults living with HIV (AWHIV) participating in clinical trials. Dolutegravir-related hepatotoxicity usually occurs in AWHIV also living with Hepatitis B or C.[17,18] In the ODYSSEY study reporting 635 person-years of CWHIV receiving dolutegravir, there was 1 report of grade 3 or higher ALT and bilirubin each.[4] Late-onset idiosyncratic ABC/DTG/3TC-related hepatitis after 3 months of therapy has been reported in AWHIV with a resolution of hepatitis after discontinuation of ABC/DTG/3TC.[18] Although uncommon, clinicians should remain aware that rare and idiosyncratic reactions can occur in CWHIV without known risk factors for DILI.

Dolutegravir inhibits the renal transporter, organic cation transporter 2, causing reduced tubular secretion of creatinine with nonprogressive increases in serum creatinine that are not associated with renal dysfunction. This phenomenon is commonly observed in adults.[19] Several cross-sectional studies show that CWHIV are at risk of mild-to-moderate renal impairment.[20–22] Serum creatinine is a crude measure of renal function affected by age, diet and exercise and may be affected by laboratory methods. To standardize measurements for serum creatinine measurements in this study, laboratories used isotope dilution mass spectrometry-traceable methodology and sites used a standard pediatric eGFR formula. Using actual values only, no grade 3 or higher serum creatinine or eGFR was observed in the study. In ODYSSEY, changes in creatinine from baseline over 96 weeks were higher for participants on both first- and second-line dolutegravir-based regimens than a standard-of-care regimen, with a slow increase over time. Mean change at 48 weeks was 0.08 and at 96 weeks 0.11 mg/dL.[4] Further study is needed on renal disease in CWHIV, including guidance for assessment of renal function in CWHIV receiving dolutegravir applicable to low-resource settings and for those cotreated with dolutegravir and tenofovir disoproxil fumarate.

Excessive weight gain on dolutegravir and other INSTI is a concern and understanding weight gain in persons with HIV is complex. In adults, it is mostly described in persons also receiving tenofovir disoproxil fumarate or tenofovir alafenamide fumarate and those initiating therapy.[23–25] There may also be a genetic risk.[25] In the REPRIEVE study, there were minimal differences in BMI in adults on INSTI-based therapy compared to other regimens after 2 years.[26] In ODYSSEY, CWHIV on dolutegravir had a larger increase in BMI over 96 weeks compared to those on standard of care, and cases of excessive weight gain are reported.[4,27] In IMPAACT 2019, an increase in mean BAZ was observed over 48

weeks. It is difficult to assess the significance of this increase given the population and study follow-up period. This increase in BAZ could indicate a return to health and as such would represent a positive outcome, particularly in naive CWHIV. However, the majority of CWHIV in this study were already on therapy and virologically controlled. Whether the increases in BAZ observed could signal future excessive weight gain and risk for future metabolic syndrome is not clear from these data. Weight gain in CWHIV should also be understood in the context of the general increase in childhood obesity including children living in lower- and middle-income countries in Asia and Africa.[28] Therapy guidance on health, nutrition, and exercise is a necessary component for standard of care. Metabolic risk in CWHIV is not determined by BMI only. Hepatic stiffness, steatosis and serum lipids improve in adolescents after switching to dolutegravir.[29]

In 350 participants on dolutegravir-based ART and 357 on nondolutegravir regimens in ODYSSEY, 15 participants had neuropsychiatric AEs: more participants on dolutegravir than nondolutegravir-containing ART reported symptoms of self-harm, life being not worth living, or suicidal thoughts.[29] The rate of neuropsychiatric AEs in the dolutegravir group was 1.91 per 1000 person-years (95% CI: 1.13–3.02) and in the standard-of-care group was 1.39 per 1000 person-years (95% CI: 0.74–2.38). The low number of events in our study may be due to the small sample, younger age of children on study, and shorter duration of follow-up. In ODYSSEY, participants experiencing neuropsychiatric events were older [median age 15.9 years (IQR: 10.4–17.5)] and on study for a median of 72 weeks.[30] We observed an increase in nightmares in IMPAACT 2019 participants; however, in ODYSSEY there was no difference between children on dolutegravir and those on nondolutegravir regimens in sleep quality.[30]

The drug interaction between rifampicin and dolutegravir remains a major concern. Data from ODYSSEY and the EMPIRICAL study confirmed that twice-daily dolutegravir overcomes the reduction in dolutegravir levels caused by drug interactions with rifampicin.[30,31] In children taking ABC/DTC/3TC, additional dolutegravir should be provided approximately 12 hours from the ABC/DTC/3TC to allow for twice-daily dolutegravir dosing.[32]

Pharmacokinetic models further strengthened the dosing recommendation for ABC/DTG/3TC formulations for children weighing ≥6 kg.[33] Children weighing <6 kg were excluded from IMPAACT 2019. Although the dolutegravir component of the dispersible FDC is sufficient in 1 tablet (5 mg), the abacavir (60 mg) and lamivudine (30 mg) dosing is below the current weight band dosing recommended by the WHO of 120 and 60 mg, respectively. Modeling data suggests a single ABC/DTG/3TC dispersible tablet would achieve acceptable pharmacokinetics levels of abacavir and lamivudine in CWHIV from 3 to <6 kg.[34] If the use of dispersible ABC/DTG/3TC FDC is endorsed in this weight band it will further simplify therapy. HLA-genotyping is not readily available in resource-constrained settings, and the risk for an abacavir hypersensitivity reaction in Africa is very low. WHO does not currently recommend testing prior to initiation of abacavir, but in communities with access and a known increased risk, testing would be prudent.

The availability of a dispersible FDC of ABC/DTG/3TC is important to simplifying dolutegravir-based ART for young CWHIV weighing 6 kg or more. Ensuring access is a priority. In collaboration with 2 generic manufacturers, a partnership involving the originator company, the Clinton Health Access Initiative, and Unitaid has facilitated the development of generic formulations to increase access.[35–37] This collaboration will help ensure access to this formulation in low- and middle-income countries, particularly where it is most needed in Africa.

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