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Realizing the Promise of Dolutegravir in Effectively Treating Children and Adolescents Living With HIV in Real-world Settings in 6 Countries in Eastern and Southern Africa

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Background: Despite encouraging results from clinical trials and in high-income countries, large-scale data on the effectiveness and safety of dolutegravir (DTG) in children and adolescents living with HIV (CALHIV) are lacking in low- and middle-income countries (LMICs).

Methods: Retrospective analysis was performed among CALHIV 0–19 years old and weighing greater than or equal to 20 kg who received DTG from 2017 to 2020 at sites in Botswana, Eswatini, Lesotho, Malawi, Tanzania and Uganda to determine effectiveness, safety and predictors of viral load suppression (VLS) among CALHIV using DTG, including through single drug substitutions (SDS).

Results: Among 9419 CALHIV using DTG, 7898 had a documented post-DTG VL, and VLS post-DTG was 93.4% (7378/7898). VLS for antiretroviral therapy (ART) initiations was 92.4% (246/263), and VLS was maintained for the ART-experienced [92.9% (7026/7560) pre- vs. 93.5% (7071/7560) post-DTG; $P = 0.14$). Among previously unsuppressed, 79.8% (426/534) achieved VLS with DTG. Only 5 patients reported a Grade 3 or 4 adverse event (0.057 per 100 patient-years) requiring DTG discontinuation. History of protease inhibitor-based ART [odds ratio (OR) = 1.53; 95% confidence interval (CI): 1.16–2.03], care in Tanzania (OR = 5.45; 95% CI: 3.41–8.70), and being 15–19 years old (OR = 1.31; 95% CI: 1.03–1.65) were associated with gain of VLS post-DTG. Predictors of VLS on DTG included VLS before DTG (OR = 3.87; 95% CI: 3.03–4.95) and using the once-daily, single tab tenofovir-lamivudine-DTG regimen (OR = 1.78; 95% CI: 1.43–2.22). SDS maintained VLS [95.9% (2032/2120) pre- vs. 95.0% (2014/2120) post-SDS with DTG; $P = 0.19$], and 83.0% (73/88) of unsuppressed gained VLS using SDS with DTG.

Conclusions: We found DTG to be highly effective and safe within our cohort of CALHIV in LMICs. These findings can empower clinicians to prescribe DTG confidently to eligible CALHIV.

Key Words: HIV/AIDS; children; adolescents; dolutegravir; LMIC

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Despite incredible advances in the treatment of HIV over the past decade, the burden of HIV/AIDS among children and adolescents living with HIV (CALHIV) remains enormous. In 2020, there was an estimated 3.4 million CALHIV 0–19 years old globally, 300,000 new HIV infections and 131,000 AIDS-related deaths among this group, the majority occurring in the eastern and southern African region.[1–3] Substantial treatment gaps,[4] disadvantages[5] and regional disparities[6] exist for CALHIV compared with their adult counterparts, with only 54% of CALHIV receiving life-saving antiretroviral therapy (ART)[7] and only 30%–68%[8,9] achieving viral load suppression (VLS).

While the unique challenges, burdens and barriers faced by CALHIV are well-described,[10–13] the lack of a robust, safe, effective and simplified ART regimen with good tolerability has been a major barrier for achieving treatment success in CALHIV. For decades, CALHIV were slow to achieve VLS as they were forced to use adult ART formulations and/or pediatric formulations with high toxicity profiles and low genetic barriers to resistance.[14] Even pediatric formulations of ritonavir-boosted lopinavir (LPV/r), a mainstay of recommended first-line ART for children for years, have numerous gastrointestinal side effects (LPV/r tablets),[15] "taste disgusting," require refrigeration, and contain alcohol (LPV/r syrup),[16] or result in large volumes of an inedible "sticky and bitter mess" (LPV/r granules),[16] ultimately being unacceptable, ineffective options for achieving VLS in large numbers of CALHIV.

A potential game changer for CALHIV is the integrase-strand inhibitor dolutegravir (DTG). Recommended in 2018 by the

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Ethical approval was obtained from Baylor College of Medicine for all sites in addition to each institutional review board in Botswana, Eswatini, Lesotho, Malawi, Tanzania and Uganda. Waiver of consent was approved by all ethics committees as this retrospective study analyzed only deidentified data.

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World Health Organization as first-line ART for all people living with HIV,[17] the advantages of DTG make it more attractive than any preceding pediatric ART.[18] DTG is very effective – with high potency, and tolerability, low toxicity and drug–drug interactions, and a high genetic barrier to resistance – and comes in a convenient, once-daily single-pill formulation, including the forthcoming 10 mg dispersible pediatric tablet. Evidence from the ODYSSEY (PENTA 20)[19] and IMPAACT P1093[20] trials, as well as experiences from high-income countries (HICs),[21–23] have shown DTG to be a superior, effective, safe and well-tolerated option among CALHIV. While these results are encouraging, they are limited to small cohorts in HICs or clinical trials, and to date, no published large-scale data exists on the use of DTG in treating CALHIV in real-world settings of low- and middle-income countries (LMICs). Such large-scale data – if reassuring – can be leveraged to encourage programs to aggressively roll out DTG globally as a life-saving treatment option for CALHIV in LMIC and beyond. To address this gap, and further strengthen the evidence base and call-to-action for using DTG in CALHIV worldwide, we evaluated the effectiveness and safety of DTG in CALHIV treated at 7 sites across 6 countries in eastern and southern Africa.

MATERIALS AND METHODS

Study Setting

The Baylor College of Medicine International Pediatric AIDS Initiative (BIPAI) Network consists of independent, affiliated nongovernmental organizations (NGOs) that provide comprehensive, patient-centered care to CALHIV through Centres of Excellence (COEs). Each COE partners with respective Ministries of Health and is staffed by interdisciplinary clinical teams. A standardized electronic medical record (EMR) system is used across all COEs. COEs included in the study were from Botswana, Eswatini, Lesotho, Malawi, Tanzania-Mbeya, Tanzania-Mwanza and Uganda.

Study Population and Study Variables

We conducted a retrospective cohort study analyzing CALHIV of 0–19 years old and weighing greater than or equal to 20 kg who received DTG as part of their HIV care between January 2017 and December 2020. The cohort included new ART initiations using a DTG-based ART and ART-experienced patients who shifted to a DTG-based regimen (irrespective of virologic status). The rollout of DTG varied across the sites, with initial availability of DTG for children beginning in 2017 (Botswana, Uganda), 2018 (Eswatini, Malawi) or 2019 (Lesotho, Tanzania). Across our sites, the initial rollout of DTG for CALHIV was targeted and supply-limited; however, by late 2018 and early 2019, DTG was more widely available and widely used for CALHIV. Available formulations of DTG were the 50 mg DTG tablet or the single tab, fixed-dose combination of tenofovir-lamivudine-DTG (TLD), which limited the use of DTG to CALHIV weighing more than 20 kg. Routine and targeted HIV viral load (VL) monitoring was done for all CALHIV across the sites, though VL testing was more limited in availability in the early years of the study compared with later years. However, routine biochemistry labs were not collected for CALHIV on DTG to monitor for drug toxicity. Per country guidelines, targeted biochemistry laboratory evaluation was only done if clinical concern for DTG toxicity. Assessment of ART drug resistance mutations via HIV genotype testing was not available as part of routine care at the COEs or pre-switch to DTG. Targeted HIV genotype testing was only sporadically available on a limited basis for CAHLIV failing second-line ART, and these results did not include information on DTG resistance. Single drug substitutions (SDS) were defined as an ART regimen change in which the nucleoside reverse transcriptase inhibitor (NRTI) backbone remained the same, and the only change was from the nonnucleoside reverse transcriptase (NNRTI) or protease inhibitor (PI) to DTG.

We extracted demographic, clinical, laboratory and ART data retrospectively using standardized structured query language scripts from the EMR system. The data extracted included COE site, age, sex, ART initiation date, ART regimen, DTG initiation date, time on ART and DTG, WHO clinical stage, TB history, nutrition status, VL testing dates and results, HIV genotype testing availability and patient outcomes. VLS was defined as VL < 1000 cps/mL.[24] Clinical and laboratory toxicities to DTG were extracted via the EMR and site-specific drug adverse events (AEs) reporting registries. AEs were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1.[25] Data quality assurance was performed to ensure validity, completeness, consistency and accuracy.

Statistical Analysis

Clinical characteristics and VLS status of participants were summarized using descriptive statistics for continuous and categorical variables. Complete case analysis using the patient's most recent VL before December 31, 2020, was used to categorize each patient as virally suppressed or unsuppressed for the comparative analysis, and those without post-DTG VL results were excluded from the VLS analyses. Comparison of categorical variables was done using the Pearson χ^2 test and Fisher's test when appropriate. A 2-sample *t* test was used to assess associations in continuous variables. Age-, sex-, site- and ART regimen-desegregated analyses were performed on the cohort with VLS being the primary outcome of interest. Logistic regression models looking at predictors of VLS as well as gain of VLS were used to produce odds ratios (OR) and 95% confidence interval (CI). Complete case analysis was used to assess any missingness within the regression models, and to allow the model to analyze those with complete covariate data. Statistical analyses were conducted using RStudio (Version 1.3.959, 2020, Integrated Development for R. RStudio, PBC, Boston, MA).

RESULTS

Cohort Characteristics

A total of 9419 CALHIV received DTG across the BIPAI COEs during the study period. This cohort represented 45.4% (9419/20,733) of all CALHIV on ART-treated at the COEs during the study period and 60.0% (9419/15,698) of all CALHIV on ART weighing 20 kg or more. The majority of CALHIV were shifted from NNRTI-based regimen, used a TLD formulation, were 50.9% female, had median age of 14.1 years and had median follow-up time post-DTG of nearly 1 year (Table 1). By study end, 96.7% (9107/9419) remained active in care, 0.1% (13/9107) were transferred out, 2.4% (227/9419) were lost to follow-up and 0.8% (72/9419) died. The average number of HIV genotype results per year per COE was 12 (range, 0–30), with no DTG resistance testing.

Effectiveness of DTG Among CALHIV

Overall, 8921 CALHIV had a documented VL pre-DTG, of which 92.7% (8273/8921) had VLS, and a total of 7898 CALHIV with a documented VL after receiving DTG, of which 93.4% (7378/7898) had VLS ($P = 0.14$). Using a cutoff of VL < 400 cps/mL, 90.9% (8110/8921) of the overall cohort pre-DTG and 91.7% (7245/7898) post-DTG achieved VL < 400 cps/mL ($P = 0.07$). Among new ART initiations with DTG with VL results (n = 263), 92.4% (243/263) achieved VLS. Analysis of only those with documented pre- and post-DTG VL (N = 7560) showed VLS

TABLE 1. Baseline Characteristics of CALHIV at Time of First Receiving DTG at BIPAI Sites in Eastern and Southern Africa From 2017 to 2020

Characteristic	CALHIV Receiving DTG (N = 9419)
Female (N, %)	4791 (50.9)
Median age at the time of DTG in years (IQR)	14.1 (11.3–16.78)
Country/site (N, %)	
Botswana	1104 (11.7)
Eswatini	1124 (11.9)
Lesotho	1119 (11.9)
Malawi	1638 (17.4)
Tanzania	1703 (18.1)
Uganda	2731 (29.0)
ART status (N, %)	
New ART initiations	401 (5.5)
Shifted from NNRTI-based regimen	5495 (75.1)
Shifted from PI-based regimen	1424 (19.5)
Median time on ART before DTG in years (IQR; N = 7170)	8.2 (5.3–11.1)
DTG regimen (N, %)	
TLD	6856 (72.8)
ABC-3TC-DTG	223 (23.7)
AZT-3TC-DTG	254 (2.7)
Third-line ART (using DTG)	76 (0.8)
History of TB disease (N, %)	43 (0.5)
WHO stage (N, %)	
I or II	4841 (51.4)
III or IV	4577 (48.6)
Nutrition status (N, %)	
Within normal limits	8694 (95.0)
Any malnutrition (mild, moderate, severe, chronic)	459 (5.0)
Median follow-up time in days after receiving DTG (IQR)	345 (208–437)

3TC indicates lamivudine; ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; BIPAI, Baylor International Pediatric AIDS Initiative; CALHIV, children and adolescents living with HIV; DTG - dolutegravir; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TB, tuberculosis; WHO, World Health Organization.

TABLE 2. Logistic Regression Model for Predictors of Gain of VL Suppression Among Previously Unsuppressed CALHIV After Shifting to DTG

Characteristic (N)	OR (95% CI)
Pre-DTG ART regimen	
NNRTI-based (n = 5700)*	1 (REF)
PI-based (n = 1457)	1.53 (1.16–2.03)
Country/Site	
Botswana (n = 903)*	1 (REF)
Eswatini (n = 1022)	1.33 (0.80–2.21)
Lesotho (n = 1042)	1.09 (0.63–1.89)
Malawi (n = 1272)	0.78 (0.45–1.35)
Tanzania (n = 922)	5.45 (3.41–8.70)
Uganda (n = 2399)	1.49 (0.92–2.43)
Age category	
0–4.99 years (n = 5)	Indet.†
5–9.99 years (n = 432)	0.69 (0.47–1.00)
10–14.99 years (n = 815)*	1 (REF)
15–19.99 years (n = 866)	1.31 (1.03–1.65)
Sex	
Female (n = 3814)	0.94 (0.75–1.17)
Male (n = 3746)*	1

*Reference Category within variable.

†Indeterminant due to small sample size and/or outcome event rate not allowing for enough power to report an OR.

ART indicates antiretroviral therapy; CALHIV, children and adolescents living with HIV; CI, Confidence Interval; DTG, dolutegravir; N/A, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; VL, viral load.

rates maintained from 92.9% (7026/7560) pre-DTG to 93.5% (7071/7560) post-DTG ($P = 0.14$), as well as at the VL < 400 cp/mL cutoff from 91.1% (6890/7560) pre-DTG to 91.8% (6942/7560) post-DTG ($P = 0.32$). VLS was maintained in 94.5% (6645/7026) of previously suppressed CALHIV following shifting to DTG-based ART. There were 79.8% (426/534) of previously unsuppressed CALHIV who achieved VLS using DTG. The following characteristics were associated with gain of VLS post-DTG among previously unsuppressed CALHIV: having used a PI-based prior ART regimen (OR = 1.53; 95% CI: 1.16–2.03), receiving care in Tanzania (OR = 5.45; 95% CI: 3.41–8.70), and being 15–19 years old (OR = 1.31; 95% CI: 1.03–1.65) (Table 2). All subgroups of previously unsuppressed CALHIV showed gains in VLS after shifting to DTG (Table 1, Supplemental Digital Content 1, http://links.lww.com/INF/E955).

Safety of DTG in Clinical Practice Among CALHIV

Only 0.07% (7/9419) of CALHIV on DTG reported a toxicity after receiving DTG requiring discontinuation of DTG. Among those 7 patients, 28.6% (2/7) experienced a Grade 1 or 2 mild AE (1 with rash and 1 with dizziness) and 71.4% (5/7) – or 0.05% of all CALHIV on DTG – experienced a Grade 3 or 4 serious AE (4 with hepatotoxicity and 1 with somnolence) (Table 2, Supplemental Digital Content 2, http://links.lww.com/INF/E956). The cohort had 8818 patient-years of observation, and an exposure-adjusted incidence rate for any AE, as well as for grade 3 or 4 AEs only, causing discontinuation of DTG of 0.079 (7 events in 8818 patient-years) and 0.057 (5 events in 8816 patient-years) per 100 patient-years, respectively. Among the 4 patients with recorded hepatotoxicity after initiating DTG, all were Grade 4 in severity, none had any known preexisting comorbidities and 3 of the 4 had full recovery of their symptoms following discontinuation of DTG. One patient (14-year-old male on ART for 9 years, fully suppressed) was transitioned to DTG and started isoniazid preventative therapy on the same visit date and developed hepatotoxicity, jaundice, nonbloody diarrhea, seizures and altered mental status 2 weeks later. He was hospitalized at a local facility and died after 2 additional weeks in the hospital with the cause of death recorded as hepatic encephalopathy by the non-COE hospital team.

Predictors of VLS Among CALHIV Using DTG-Based ART

Logistic regression models found that being virally suppressed before shifting to DTG-based regimen (OR = 3.87; 95% CI: 3.03–4.95) and using the once-daily, single tab TLD regimen (OR = 1.78; 95% CI: 1.43–2.22) were predictors of VLS among CALHIV using DTG, whereas each increase in a year of age slightly decreased the odds of gaining VLS (OR = 0.94; 95% CI: 0.91–0.97) (Table 3). No statistically significant differences in VLS were seen based on sex, average time on ART before DTG, malnutrition status or history of TB disease.

Effectiveness of SDS With DTG in CALHIV

A total of 2665 CALHIV, or 28.2% (2665/9419) of the total DTG cohort, received DTG through SDS. The NRTI backbone in the SDS was abacavir-based in 44.4% (1180/2665), tenofovir-based in 38.9% (1032/2665) and zidovudine-based in 16.7% (443/2665). Among the SDS cohort with pre- and post-DTG VLs results (n = 2120), VLS was maintained using SDS, with no statistically significant loss of VLS overall [95.9% (2032/2120) vs. 95.0% (2014/2120); $P = 0.19$]. Logistic regression models for gain of VLS among the previously unsuppressed SDS cohort showed

TABLE 3. Logistic Regression Model for Predictors of VLS in All CALHIV Using DTG-Based ART

Characteristic	OR (95% CI)
Female	0.97 (0.80–1.17)
Average age (SD) in years	0.94 (0.91–0.97)
Average time on ART before DTG (SD) in years	0.99 (0.96–1.01)
Virally suppressed before DTG	3.87 (3.02–4.95)
Any malnutrition	1.03 (0.60–1.77)
History of TB disease	1.58 (0.35–7.16)
Using single tab TLD regimen	1.78 (1.43–2.22)

ART indicates antiretroviral therapy; CALHIV, children and adolescents living with HIV; CI, confidence interval; DTG, dolutegravir; OR, odds ratio; SD, standard deviation; TB, tuberculosis; TLD, tenofovir-lamivudine-dolutegravir fixed drug combination.

TABLE 4. Logistic Regression Model for Predictors of Gain of VL Suppression Among Previously Unsuppressed CALHIV After Shifting to DTG Using SDS With DTG

Characteristic (N)	OR (95% CI)
Pre-DTG ART regimen	
TLE → TLD (n = 590)*	1
TDF-3TC-PI →TLD (n = 214)	1.36 (0.55–3.36)
ABC-3TC-NNRTI → ABC-3TC-DTG (n = 560)	0.66 (0.26–1.66)
ABC-3TC-PI → ABC-3TC-DTG (n = 370)	1.05 (0.42–2.61)
Country/Site	
Botswana (n = 90)*	1
Eswatini (n = 246)	Indet.†
Lesotho (n = 206)	0.16 (0.03–0.86)
Malawi (n = 340)	0.38 (0.13–1.12)
Tanzania (n = 248)	1.57 (0.58–4.23)
Uganda (n = 604)	0.49 (0.19–1.29)
Age category	
0–4.99 years (n = 4)	Indet.†
5–9.99 years (n = 356)	0.75 (0.36–1.54)
10–14.99 years (n = 571) *	1 (REF)
15–19.99 years (n = 803)	0.60 (0.28–1.27)
Sex	
Female (n = 1021)	0.99 (0.58–1.68)
Male (n = 713)*	1

*Reference Category within variable.

†Indeterminant due to small sample size and/or outcome event rate not allowing for enough power to report an OR.

ART indicates antiretroviral therapy; CALHIV, children and adolescents living with HIV; CI, confidence interval; DTG, dolutegravir; N/A, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; SDS, single drug substitution; VL, viral load.

heterogeneity across geographic sites, but no significant differences based on NRTI backbone, pre-DTG ART anchor drug (ie, NNRTI vs. PI), or age or sex (Table 4). There were 83.0% (73/88) of previously unsuppressed CALHIV who gained VLS after SDS with DTG (Table 3, Supplemental Digital Content 3, http://links.lww.com/INF/E957). Similarly, being virally suppressed before SDS with DTG (OR = 3.16; 95% CI: 1.68–5.94) and using the once-daily, single tab TLD regimen (OR = 2.02; 95% CI: 1.27–3.19) were again predictors of VLS among SDS with DTG CALHIV cohort, whereas younger CAHLIV utilizing SDS with DTG were less likely to achieve VLS compared with their older counterparts (OR = 0.90; 95% CI: 0.84–0.96) (Table 5).

TABLE 5. Logistic Regression Model for Predictors of VLS in All CALHIV Using an SDS With DTG

Characteristic	OR (95% CI)
Female	0.87 (0.60–1.28)
Average age in years	0.90 (0.84–0.96)
Average time on ART before DTG in years	0.99 (0.94–1.04)
Virally suppressed before DTG	3.16 (1.68–5.94)
Any malnutrition	0.70 (0.27–1.82)
History of TB disease	Indet.*
Using single tab TLD regimen	2.02 (1.27–3.19)

*Indeterminant due to small sample size and/or outcome event rate not allowing for enough power to report an OR.

ART indicates antiretroviral therapy; CALHIV, children and adolescents living with HIV; CI, confidence interval; DTG, dolutegravir; OR, odds ratio; SDS, single drug substitution; TB, tuberculosis; TLD, tenofovir-lamivudine-dolutegravir fixed drug combination.

DISCUSSION

We present one of the largest real-world analyses of the effectiveness and safety of DTG use in CALHIV living in eastern and southern Africa, covering a 4-year period that included 9419 CALHIV and 8818 patient-years. Overall, DTG was extremely effective, with 93.4% (7378/7898) of CALHIV achieving VLS, and only 0.8% (72/9419) of the cohort experiencing death. Impressive VLS rates were seen for ART-naïve and ART-experienced patients, as well as across sites, age groups and sexes. Not only were high VLS rates maintained among those previously virally suppressed on non-DTG regimens, but remarkably, nearly 80% of CALHIV who were unsuppressed on a non-DTG regimen – despite the best, most intensive treatment and adherence support efforts – were able to become virally suppressed after switching to a DTG regimen, though heterogeneity across sites was seen. This highlights how the simple intervention of optimizing a child's or adolescent's ART with a high potency, well-tolerated anchor drug like DTG was able to achieve treatment success where a multitude of time- and resource-intensive psychosocial interventions could not. In our cohort, DTG was found to be particularly effective for achieving VLS when used as the single pill, once-daily TLD formulation as well as when used as SDS (95.0% achieving VLS), including those without VLS before shifting to SDS with DTG. Equally important, DTG was found to be very safe in our cohort, with only 5 patients experiencing a Grade 3 or 4 AE requiring DTG discontinuation (0.057 per 100 patient-years), only 7 patients total with any AEs requiring DTG discontinuation during the study period (0.079 per 100 patient-years), and only 1 of the AE patients experiencing death.

Our findings of 91.7% of CALHIV using DTG having VL < 400 cps/mL were similar to clinical trial findings of both the IMPAACT P1093 study where 74% of 12–18 years old achieved VL < 400 cps/mL at 48 weeks[26] and the ODYSSEY (PENTA 20) study[19] where 89% of 2–18 years old achieved VL < 400 cps/mL at 96 weeks. It also compared favorably to multiple HIC settings where VLS rates among CALHIV on DTG varied from 66%[27] to 74%[22] to 88%.[21] The treatment success of DTG experienced by our cohort was encouraging as all too often CALHIV in LMICs have limited access to new, optimal ART formulations,[28] missed opportunities for regimen switching,[29] and remain disproportionally disadvantaged compared with adult or HIC counterparts. Our cohort is a strong reminder of the treatment success that can be achieved in CALHIV with timely, widespread, and sustained use of DTG in CALHIV in LMICs.

The impressive safety profile of DTG and low incidence of serious AEs seen within our cohort adds to the growing consensus that DTG is extremely safe for use in children and adolescents. The favorable safety profile of DTG has long been recognized in adults,[30] and results from the ODYSSEY (PENTA 20),[19] IMPACT P1093[20] and HIC cohorts[21,22] also reported low rates of AE and

discontinuations of DTG in children and adolescents. While routine laboratory monitoring was not available in our cohort, serious Grade 3 or 4 AEs were only seen at a rate of 0.057 per 100 patient-years (5 events in 8816 patient-years) and contributed to 1 death. Mild Grade 1 or 2 AEs were an infrequent cause of discontinuation of DTG, likely because these AEs can often be managed supportively or through lifestyle changes without requiring discontinuation of DTG. For example, while weight gain in CALHIV receiving DTG has recently received attention through retrospective cohort studies,[31] it was not a cause for discontinuation of DTG in any CALHIV in our cohort and findings from the ODYSSEY trial also reassuringly demonstrated that DTG-based ART was not associated with excessive weight gain among children and adolescents.[32]

Our findings offer support for programmatic switching to DTG in settings where pre-switch VL or HIV resistance testing is not feasible as part of ART optimization strategies for CALHIV.[14,29,33] Despite our sites not having routine access to HIV resistance, post-DTG VLS rates were impressive at more than 90%. Similar VLS rates were observed in our SDS cohort and 83% (73/88) of unsuppressed CALHIV were able to achieve VLS with an SDS using DTG. Multiple studies have found that the presence of M184V/I or other NRTI resistance-associated mutations (RAM), does not increase the risk of or have an impact on virological failure after switching to DTG,[34–36] including in LMIC settings.[33] Further, DTG plus lamivudine as dual therapy has demonstrated success in achieving VLS and cost-effectiveness in numerous studies.[37,38] Clinician hesitancy to changing ART can have dire consequences to patients,[39] and these findings will help to quell concerns that preexisting NRTI RAMs may adversely affect the ability of DTG to achieve VLS in CALHIV, and empower providers in LMICs to confidently switch their pediatric and adolescent patients to DTG.

Our study has several limitations to consider when interpreting results. Our retrospective dataset was missing documented pre-DTG VLs in 5.3% (498/9419) and post-DTG VLs in 16.1% (1516/9419) of the cohort, reflecting real-world practices and challenges of VL testing in our settings. It is possible that those with missing post-DTG VLs could be more likely to have poor adherence, lost to follow-up and/or treatment failure. If CALHIV with missing VL data were more likely to be failing treatment then the estimates and true treatment failure rates in our cohort may be higher. Our retrospective analysis also reported high VLS rates pre-DTG in the cohort and no difference in VLS rates pre- and post-DTG in the full cohort, highlighting the potential for selection bias. This is likely due to the adoption of DTG rollout across national ART guidelines, which first prioritized DTG in those with VLS and new ART initiations. Routine HIV resistance testing was also unavailable, preventing any conclusions about the impact of NRTI or INSTI RAMs on DTG effectiveness. Our analysis also did not include data on adherence or psychosocial determinants of adherence, which are well-known predictors of VLS. Despite the impressive "regimen forgiveness" of DTG, high levels of poor adherence of even the most robust ART will result in poor treatment outcomes, and continued strengthening of person-centered care to support adherence is needed. In addition, the BIPAI network of COEs may be more well-staffed, well-resourced and offer a wider array of services than other HIV clinics in the region or other LMICs. Our findings, therefore, may not be representative of other HIV clinics, particularly when compared with more rural and understaffed facilities. Finally, we were unable to assess for the impact of the COVID-19 pandemic on our cohort during 2020. The COVID-19 pandemic and subsequent lockdown measures caused massive disruptions to medical supply chains, laboratory services, public transportation, schooling, economical livelihood and HIV care worldwide and within eastern and southern Africa and may have explained some of the heterogeneity observed across our study sites.

CONCLUSIONS

This multicountry analysis of 9419 CALHIV treated with DTG across 6 countries in eastern and southern Africa demonstrated that DTG was both highly effective and safe for CALHIV. DTG was effective for CALHIV in real-world settings among ART-naïve and ART-experienced, virally suppressed and unsuppressed, when used as an SDS, and across geographic settings, age groups and sexes in CALHIV. These findings highlight the many advantages of DTG to pediatric and adolescent patients, their caregivers, healthcare providers and healthcare systems, and strengthen the ART optimization call for "universal DTG for CALHIV," especially as LMICs improve access to DTG and prepare to receive the 10 mg dispersible formulations of DTG in 2022 and beyond. Clinicians should feel empowered to prescribe DTG to all eligible CALHIV as one of the most effective and safe ART options currently available.

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