Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide in adolescents and children with HIV: week 48 results of a single-arm, open-label, multicentre, phase 2/3 trial

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Summary

Background Bictegravir is a potent integrase strand-transfer inhibitor (INSTI) with a high genetic barrier to resistance. Bictegravir, coformulated with emtricitabine and tenofovir alafenamide, is recommended by key European and US HIV treatment guidelines as the preferred single-tablet regimen for adults and adolescents. The aim of this study was to assess the pharmacokinetics, safety, and efficacy of switching to this regimen in virologically suppressed children and adolescents with HIV.

Methods In this single-arm, open-label trial, we enrolled virologically suppressed children and adolescents (aged 6 to <18 years) with HIV at 22 hospital clinics in South Africa, Thailand, Uganda, and the USA. Eligible participants had a bodyweight of at least 25 kg, were virologically suppressed (HIV-1 RNA <50 copies per mL) on a stable ART regimen for at least 6 months before screening, had a CD4 count of at least 200 cells per µL, and an estimated glomerular filtration rate of at least 90 mL/min per 1·73 m² by the Schwartz formula at screening. All participants received the fixed-dose regimen of coformulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg once daily. Pharmacokinetic analysis was used for dosing confirmation, and results compared with adult values. The primary outcomes were area under the curve at the end of the dosing interval (AUC_{tau}) and concentration at the end of the dosing interval (C_{tau}) of bictegravir, and incidence of treatment-emergent adverse events and laboratory abnormalities at week 24. Efficacy and safety analyses included all participants who received at least one dose of study drug. We report the 48-week results. This study is registered with ClinicalTrials.gov, NCT02881320.

Findings Between Sept 29, 2016 and Feb 16, 2018, we enrolled 102 participants. 100 participants received bictegravir, emtricitabine, and tenofovir alafenamide (cohort 1 [adolescents aged 12 to <18 years], n=50; cohort 2 [children aged 6 to <12 years], n=50). The mean bictegravir AUC_{tau} was 89 100 ng×h/mL (coefficient of variation 31·0%) in adolescents (cohort 1) and 128 000 ng×h/mL (27·8%) in children (cohort 2). Compared with adults, bictegravir C_{tau} was 35% lower in adolescents and 11% lower in children. The 90% CIs of both parameters were within the predefined pharmacokinetic equivalence boundary and within overall range of exposures observed in adults and deemed to be safe and efficacious (geometric least-squares mean ratio [GLSM] 86·3% [90% CI 80·0–93·0] for AUC_{tau} and 65·4% [58·3–73·3] for C_{tau} in adolescents; GLSM 125% [90% CI 117–134] for AUC_{tau} and 88·9% [80·6–98·0] for C_{tau} for children). Bictegravir, emtricitabine, and tenofovir alafenamide was well tolerated; most adverse events were grade 2 or less in severity and no study drug-related serious adverse events were reported. One participant discontinued study drug due to adverse events (grade 2 insomnia and anxiety). Virological suppression (HIV-1 RNA <50 copies per mL) was maintained by all 100 participants at week 24 and by 98 (98%) of 100 at week 48; no participants had treatment-emergent resistance.

Interpretation In adolescents and children with HIV, the bictegravir, emtricitabine, and tenofovir alafenamide single-tablet regimen was well tolerated and maintained virological suppression. Our data support the treatment of HIV in adolescents and children with this single-tablet regimen. At present, the single-tablet regimen is recommended as first-line treatment in the USA for adolescents and as an alternative regimen in children and has the potential to represent an important regimen in the paediatric population.

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Introduction

The aim of antiretroviral therapy (ART) in children and adolescents with HIV is to optimise immunological outcomes via virological suppression while maintaining overall wellbeing. Children and adolescents receiving ART with high treatment tolerance are the most likely to

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Research in context

Evidence before this study

Integrase strand-transfer inhibitors (INSTIs) are the preferred third agents within a complete antiviral regimen for treatment of HIV in children globally. Coformulated emtricitabine and tenofovir alafenamide is a preferred component in antiretroviral regimens for children in the USA and the European Union. Data in adult populations support the use of fixed-dose combinations for the treatment of HIV; single-tablet regimens are recommended for enhancement of adherence and are also considered optimum for children. Many fixed-dose combinations recommended for adults are also recommended for adolescents, but not for children (especially those with bodyweight <25 kg) due to weight restrictions. Approval for these fixed-dose combinations have mainly been based on data derived from use of the individual components in participants included in paediatric studies rather than from the fixed-dose product itself. We searched PubMed for articles published between Jan 1, 1997, and Sept 30, 2020, using each of the search terms "tenofovir alafenamide" or "bictegravir", "children", "adolescent" or "pediatric", "trial" or "study", limited to English language articles. The search yielded two articles on the safety, efficacy, and pharmacokinetics of the single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide: one study in 50 treatment-naive adolescents with HIV (aged 12 to <18 years) at week 48 and another study in 23 virologically suppressed children (aged 6 to <12 years) at week 24. Results of these studies showed that this single-tablet regimen was safe, well tolerated, and maintained high rates of virological efficacy in children and adolescents. Our search identified no articles of the fixed-dose combination containing bictegravir, emtricitabine, and tenofovir alafenamide in children and adolescents.

Added value of this study

This is the first report of pharmacokinetic, safety, and efficacy data for the single-tablet regimen containing bictegravir coformulated with emtricitabine and tenofovir alafenamide, given once daily for 48 weeks in paediatric participants (aged 6 to <18 years) with a bodyweight of at least 25 kg. In our study, population pharmacokinetic modelling showed that the area under the curve at the end of the dosing interval (AUC_{tau}) and maximum plasma concentration (C_{max}) of bictegravir in adolescents were similar to that in adults, and bictegravir concentrations at the end of the dosing interval [C_{tau}]) were slightly lower than adults, but were markedly higher than the half-maximal inhibitory concentration. In children (aged 6 to <12 years), bictegravir AUC_{tau} and C_{max} values were modestly higher than those of adults and C_{tau} levels were similar to those of adults. Adherence was high and consistent with the acceptability of the tablet.

Implications of all the available evidence

The pharmacokinetics, safety, and tolerability of coformulated bictegravir, emtricitabine, and tenofovir alafenamide given as a single-tablet regimen in children and adolescents with HIV (aged 6 to <18 years with bodyweight ≥25 kg) informed the US Food and Drug Administration approval for this group in the USA. The findings of this study support ongoing paediatric drug development of this treatment regimen at lower doses for younger children.

achieve these goals. Integrase strand-transfer inhibitors (INSTIs) have demonstrated few off-target effects and are recommended first-line agents in the USA and European Union for adolescents and children.[1–3]

Bictegravir is an INSTI with a high genetic barrier to resistance and low potential for drug–drug interactions.[4,5] Bictegravir is associated with few drug–drug interactions with one notable exception: administration with rifampin decreases bictegravir concentrations, which are occassionally reduced below levels known to be efficacious.[6] Bictegravir 50 mg is coformulated with emtricitabine 200 mg and tenofovir alafenamide 25 mg as a single-tablet regimen. Tenofovir alafenamide has a favourable bone and renal safety profile when compared with tenofovir disoproxil fumarate,[7,8] which is important in growing children. In adults, the bictegravir, emtricitabine, and tenofovir alafenamide single-tablet regimen results in high virological suppression rates with a favourable safety profile,[9–12] and is currently approved in multiple regions for adults, and in the USA and Brazil for adolescents and children (aged 6 to <18 years with bodyweight ≥25 kg).[13,14] The regimen is recommended by key European and US HIV Treatment Guidelines as the preferred single-tablet regimen for adults and adolescents.[2,15,16] The approved tablet of bictegravir, emtricitabine, and tenofovir alafenamide is small in size (15 mm×8 mm). Comparatively, larger tablet sizes are reported for abacavir, emtricitabine, and dolutegravir (22 mm×11 mm) and elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (19 mm×9 mm).

Fixed-dose combinations are considered optimum for paediatric ART worldwide and are associated with improved adherence.[17–22] Optimising adherence to sustain virological control is crucial for children who require lifelong therapy. Adolescents with HIV also greatly benefit from regimen simplification using fixed-dose combination ART whether infected perinatally or later in life, since adherence challenges are numerous during this stage of life.[23,24]

Pharmacokinetic parameters can be used to predict the efficacy of an antiretroviral in a paediatric population with HIV on the basis of the drug's efficacy in adults. Similar exposures (within a given bioequivalence range) to particular efficacy-associated analytes in both populations suggest that efficacy is likely to be similar. Thus,

pharmacokinetic parameters are often used as primary endpoints in paediatric studies of antiretrovirals.

We report the 48-week pharmacokinetic, safety, and efficacy data for the coformulated bictegravir, emtricitabine, and tenofovir alafenamide combination in children and adolescents (aged 6 to <18 years).

Methods

Study design and participants

GS-US-380-1474 is an open-label, single-arm, two-part trial done at 22 hospital clinics in South Africa, Thailand, Uganda, and the USA. This study was designed as a phase 2/3 trial since bictegravir, emtricitabine, and tenofovir alafenamide was being assessed in a novel population (ie, paediatric) and the study follows phase 3 results from four adult studies comprising 2414 participants.[13,14] Eligible participants were children and adolescents (aged 6 to <18 years), had a bodyweight of at least 25 kg, and were virologically suppressed (HIV-1 RNA <50 copies per mL) on a stable regimen for at least 6 months before screening (defined as an antiretroviral regimen that has not changed in 180 consecutive days). The stable regimen must have consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third drug. Eligible participants also had a CD4 count of at least 200 cells per µL and an estimated glomerular filtration rate (eGFR) of at least 90 mL/min per 1·73 m² by the Schwartz formula at screening. Participants must have also had no documented or suspected resistance to emtricitabine, tenofovir, or INSTIs including, but not limited to, the reverse transcriptase resistance mutations, Lys65Arg and Met184Val/Ile.

This study had two parts: part A was used as a dose-confirmation component and part B was used to assess safety and efficacy. Eligible participants were grouped into two cohorts on the basis of age and bodyweight: adolescents (aged 12 to <18 years) who weighed at least 35 kg were included in cohort 1 and children (aged 6 to <12 years) who weighed at least 25 kg were included in cohort 2. Cohorts were enrolled sequentially into the dose-confirmation component of the study (part A). A review of intensive pharmacokinetic data and short-term safety data for cohort 1 by an independent data monitoring committee triggered enrolment of new participants into cohort 2 (part A) and additional participants into cohort 1 (part B). Additional participants could enrol into cohort 2 (part B) for assessment of safety and efficacy after a second data monitoring committee reviewed pharmacokinetic and safety data for cohort 2 participants (part A).

This trial was done in accordance with the Declaration of Helsinki and was approved by central or site-specific review boards or ethics committees. All participants provided written or oral assent in their native languages, and their parents or caregivers provided written informed consent.

Procedures

Eligible participants received an oral once-daily regimen of coformulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg. The regimen was given regardless of food intake.

Post-baseline study visits were done at weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48. After week 48, participants were given the option to continue receiving bictegravir, emtricitabine, and tenofovir alafenamide in an open-label extension phase, during which study visits were done every 12 weeks. Study drug was made available to participants in the extension phase until it became commercially available and accessible to the participant as approved by ethics committees at each site.

Laboratory tests, done at screening, pre-baseline, and post-baseline, included haematological analysis, serum chemistry tests, fasting lipid parameters, CD4 cell counts, eGFR (calculated using the Schwartz formula; Covance Laboratories, Indianapolis, IN, USA), and measurement of plasma HIV-1 RNA (Roche TaqMan 2.0 [Roche Diagnostics, Rotkreuz, Switzerland]). Participants with confirmed plasma HIV-1 RNA 50 copies or higher per mL (with a second sample with confirmed plasma HIV-1 RNA of 200 copies per mL or higher) or plasma HIV-1 RNA levels of 200 copies per mL or higher in the week 48 window, or at the last visit on study drug, had their plasma HIV-1 RNA sample tested for the development of resistance. Protocol-defined resistance testing consisted of genotypic Sanger sequencing and phenotypic analysis of integrase, protease, and reverse transcriptase (Monogram Biosciences, San Francisco, CA, USA). Pre-existing drug resistance was assessed using available historical genotypes or retrospective proviral DNA genotyping of baseline samples from participants who qualified for resistance testing using the GenoSure Archive assay (Monogram Biosciences).

Safety was assessed by physical examinations, Tanner stage assessments, laboratory tests, concomitant drugs, and recording of adverse events, which were coded using the Medical Dictionary for Regulatory Activities (version 22·0). Adverse events and laboratory abnormalities were graded according to a modified version of the Division of AIDS guidelines (version 2.1).[25]

In part A, the pharmacokinetics of bictegravir, emtricitabine, and tenofovir alafenamide were assessed in an intensive pharmacokinetic substudy (cohort 1, n=24; cohort 2, n=25), consisting of post-dose pharmacokinetic blood samples obtained at 30 min, and 1, 2, 3, 4, 6, 8, and 24 h after an observed dose given at the clinic. Additionally, for all participants in part A and part B, based on the cohort, the trough pharmacokinetic blood sample (ie, the lowest concentration reached by the drug before the next dose was given) was obtained at on-treatment study visits (1, 2, 3, 8, 12, 16, 24, 36, and 48 weeks) with samples collected 20–28 h after participants had a dose of study drug. Plasma concentrations of bictegravir, emtricitabine, and tenofovir alafenamide were determined using fully

validated high performance liquid chromatography tandem mass spectroscopy bioanalytical methods at QPS (Newark, DE, USA). The investigator (or designee) also used age-appropriate questions to ascertain palatability (taste) and acceptability (acceptable product shape and size) of the tablet. Adherence was assessed by pill count ascertained from returned bottles between baseline and last study visit.

Outcomes

The primary endpoints were the pharmacokinetic parameters of area under the curve (AUC) at the end of the dosing interval (AUC_{tau}) and the observed concentrations at the end of the dosing interval (C_{tau}) for bictegravir at steady state at weeks 2 and 4 for cohorts 1 and 2, and safety and tolerability as measured by the incidence of treatment-emergent adverse events and laboratory abnormalities at week 24. Secondary endpoints were the proportion of participants who had maintained virological suppression (HIV-1 RNA <50 copies per mL) at weeks 24 and 48, as defined by the FDA-defined snapshot algorithm;[26] pharmacokinetic parameters (maximum plasma concentration [C_{max}] and time of C_{max} [T_{max}]) for bictegravir; AUC_{tau}, C_{max}, and C_{tau} for tenofovir alafenamide and emtricitabine, as applicable; change from baseline in CD4 cell count and percentage change at weeks 24 and 48; incidence of treatment-emergent adverse events and laboratory abnormalities at week 48; and acceptability and palatability of the full-strength bictegravir, emtricitabine, and tenofovir alafenamide formulation.

Statistical analysis

A minimum of 12 participants per cohort in part A were anticipated to provide 98% power to conclude bictegravir AUC_{tau} and 94% power to conclude bictegravir C_{tau} equivalence in adolescent participants and in children versus adults (approximately 22 participants from adults in historical phase 2 study[27]). We assumed that the expected geometric least-squares mean (GLSM) ratio of bictegravir AUC_{tau} and C_{tau} between paediatric participants and adult participants was 1, with an equivalency boundary of 70–143%, two one-sided tests each with α=0·05, a SD of AUC_{tau} of 0·19 ng×h per mL, and a SD of C_{tau} of 0·27 ng/mL (natural log scale). Additional details on sample size and power calculations are provided in the appendix (p 2).

The analyses for this report were done after all enrolled participants had completed their week 48 study visit or had prematurely discontinued the study drug.

Bictegravir and tenofovir alafenamide exposures were estimated using population phramacokinetic analyses. We used pharmacokinetic compartmental models, which coupled non-linear mixed-effect models with ordinary differential equations describing the flow of drug concentration between compartments.[28] The model to describe bictegravir pharmacokinetics in children and adolescents was a one-compartment model with first-order absorption, first-order elimination from the central compartment and a lag time, interindividual variability on apparent oral clearance, apparent peripheral volume, and first order absorption rate constant (k_a), covariance on oral clearance and apparent peripheral volume, an additive error model (for log-transformed data), and inter-occasion variability on oral clearance and apparent peripheral volume.

The final model to describe tenofovir alafenamide pharmacokinetics in children and adolescents was a two-compartment model with the M3 method, zero order input with first order absorption, linear elimination, interindividual variability terms on oral clearance, apparent peripheral volume, k_a, and loading dose, and covariance on oral clearance and apparent peripheral volume, k_a and loading dose, with a proportional error model (for log-transformed data). Additional details regarding the pharmacokinetic compartmental models are provided in the appendix (pp 2–5).

Using the developed population pharmacokinetic models, the pharmacokinetic concentration-time profile for each participant was simulated at steady-state for each analyte via an ordinary differential equation solver. Based on the simulated steady-state concentration profile, the endpoint of AUC_{tau} was computed using trapezoidal rule to obtain the area under the concentration profile curve over the dosing interval, and C_{max} was obtained based on the maximum concentration attained in the simulated concentration profile.

Emtricitabine exposures were calculated from intensive pharmacokinetic data in paediatric groups in the current study.[13,14]

Predicted systemic exposures of bictegravir and tenofovir alafenamide in adolescents weighing at least 35 kg and children weighing at least 25 kg given bictegravir, emtricitabine, and tenofovir alafenamide were compared with those from adults with HIV who participated in four phase 3 studies evaluating the same regimen and formulation (n=1193).[13,14] For bictegravir, an ANOVA model was fitted to the natural logarithm-transformed values of AUC_{tau} and C_{tau}; as the primary endpoints) and C_{max} (as the secondary endpoint), with treatment group as a fixed effect, by cohort. Treatment groups were defined as test treatment (paediatric participants in this study) and reference treatment (adults in historical studies). The pharmacokinetic parameters AUC_{tau}, C_{max}, and C_{tau} for emtricitabine, and AUC_{tau} and C_{max} for tenofovir alafenamide were analysed using the same methods. C_{tau} was not reported for tenofovir alafenamide, which has a short half-life and is not detectable at the end of the dosing interval, which precludes estimation of C_{tau}.

See Online for appendix

For bictegravir, emtricitabine, and tenofovir alafenamide, 90% CIs for the GLSM ratios of the test and reference treatments were calculated for AUC_{tau}, C_{max}, and C_{tau} by cohort, as applicable. Equivalency in pharmacokinetics was concluded if the 90% CIs were within the equivalence

boundaries of 70–143%. Additional details on the statistical comparative analyses are provided in the appendix (pp 5–6).

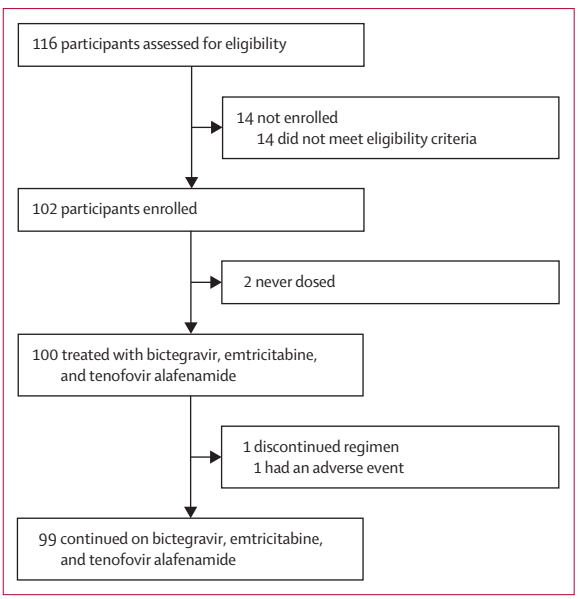

Figure: **Trial profile**

	Cohort 1 (age 12 to <18 years; n=50)	Cohort 2 (age 6 to <12 years; n=50)
Median age, years (range)	15 (12 to 17)	10 (6 to 11)
Sex		
Female	32 (64%)	27 (54%)
Male	18 (36%)	23 (46%)
Race*		
Asian	13 (27%)	11 (22%)
Black	32 (65%)	36 (72%)
Native Hawaiian or Pacific Islander	1 (2%)	0
White	1 (2%)	2 (4%)
Other	2 (4%)	1 (2%)
Hispanic or Latino	2 (4%)	0
Weight, kg	44·8 (40·0 to 56·1)	29·0 (26·9 to 32·5)
Weight Z score	−0·54 (−1·55 to 0·39)	−0·35 (−1·30 to 0·45)
Height, cm	155·5 (148·5 to 159·0)	133·3 (129·5 to 139·5)
Height Z score	−0·87 (−1·62 to −0·41)	−0·67 (−1·27 to 0·01)
eGFR (Schwartz), mL/min per 1·73 m²	145·0 (134·0 to 170·0)	153·5 (144·0 to 173·0)
Tanner stage†		
Male participants with available data, n	18	23
Stage 1–3	10/18 (56%)	23/23 (100%)
Stage 4–5	8/18 (44%)	0
Female participants with available data, n	32	27
Stage 1–3	11/32 (34%)	27/27 (100%)
Stage 4–5	21/32 (66%)	0
HIV-1 RNA <50 copies per mL	50 (100%)	50 (100%)
CD4 count, cells per µL	750 (586 to 926)	898 (707 to 1121)

(Table 1 continues on next page)

All participants who received at least one dose of study drug were included in the efficacy analysis. For the snapshot analysis, participants were classified on the basis of three outcomes: plasma HIV-1 RNA 50 copies per mL or higher at week 24 or 48 (days 141–210, inclusive) or week 48 (days 295–378, inclusive), participants who discontinued study drug due to reasons other than absence of efficacy before or at week 24 or 48 with last plasma HIV-1 RNA 50 copies per mL or higher, and participants who discontinued study drug before or at week 48 due to absence of efficacy); plasma HIV-1 RNA 50 copies per mL or less at week 24 or 48; and no virological data in the week 24 or 48 window (participants who discontinued study drug due to reasons other than absence of efficacy before or at week 24 or 48 with last available plasma HIV-1 RNA <50 copies per mL, and participants who remained on study drug with missing plasma HIV-1 RNA data at week 24 or 48). Change from baseline in CD4 cell count and percentage at weeks 24 and 48 were summarised by treatment group with descriptive statistics based on the full analysis set.

We summarised baseline characteristics with descriptive statistics for the safety analysis set, which included all participants who received at least one dose of study drug. Safety data were integrated across the two cohorts and summarised using descriptive statistics. Safety data are described using all data collected on or after study drug was first given until either the data cutoff date or, for participants who discontinued treatment early, up to 30 days after the last dose of study drug. Tanner stage assessments were used to evaluate the onset and progression of pubertal changes. Bodyweight, weight Z score, height, and height Z score were summarised.

This study is registered with ClinicalTrials.gov, NCT02881320.

Role of the funding source

The study funder had the lead role in study design, data collection, data analysis, data interpretation, and writing of the manuscript.

Results

Between Sept 29, 2016, and Feb 16, 2018, 102 participants were enrolled, of whom 100 received at least one dose of study drug and thus were included in the full analysis set (figure). This analysis includes data collected up to June 21, 2019. At the time of data cutoff for this analysis, 100 participants had been treated with bictegravir, emtricitabine, and tenofovir alafenamide and 99 had completed the 48-week main phase. One participant discontinued study drug due to adverse events. Median age was 12 years (range 6–17), median weight was 38·9 kg (range 25·0–122·8), 59 (59%) of 100 participants were female, and most were black (68 [68%]) or Asian (24 [24%]; table 1). Most participants had acquired HIV perinatally (93 [93%] of 100 participants), and 93 [93%] of

100 participants had no HIV symptoms or AIDS at baseline. The median time since HIV diagnosis was 11 years (range 2–17). Previous antiretroviral regimens are listed in the appendix (p 7).

Population pharmacokinetics of bictegravir were assessed using data collected from intensive pharmacokinetic sampling (ie, involving a series of blood samples from each participant over time) in part A for each cohort, and sparse pharmacokinetic sampling in all participants in parts A and B (table 2). For cohort 1 (adolescents aged 12 to <18 years), the bictegravir AUC_{tau} GLSM ratio (86·3% [90% CI 80·0–93·0]) was within the associated 90% CIs of the predefined pharmacokinetic equivalence boundary (70–143%). Bictegravir C_{tau} was 35% lower in this cohort than in adults. The bictegravir AUC_{tau} and C_{tau} GLSM ratios were also within the pharmacokinetic equivalence boundary for cohort 2 (children aged 6 to <12 years; table 2).

Tenofovir alafenamide and emtricitabine exposures in adolescents were similar to those in adults (table 2). In children, tenofovir alafenamide AUC_{tau} was 83% higher and C_{max} was 53% higher than adults. Mean emtricitabine AUC_{tau} was 43% higher and C_{max} was 85% higher in children than in adults. Although tenofovir alafenamide and emtricitabine exposures exceeded the upper limit of the equivalence boundary, the exposures were within the range of safe exposures obtained from adults and children.

Median study drug adherence was 99%, and 76 (76%) of 100 participants had more than 95% adherence. No participants reported issues with the palatability of study drug and product shape or size (acceptability).

The median exposure to study drug was 80 weeks (IQR 66–82) and the single-tablet regimen was well tolerated. Most adverse events were mild or moderate in severity (table 3). The most common adverse events were upper respiratory tract infection (26 [26%] of 100 participants) and diarrhoea (11 [11%]). Most events were common childhood infections or gastrointestinal adverse events. No participants died or had study drug-related serious adverse events. A 7-year-old female participant weighing 25·5 kg at baseline, who had a previous medical history of anxiety and neuropsychiatric changes after receiving raltegravir, discontinued the study at week 20 due to grade 2 insomnia and anxiety, which was considered by the investigator to be related to treatment. At week 16, this participant had a trough bictegravir concentration of 3060 ng/mL, which was within the mean (SD) for cohort 2 at that timepoint (202736 ng/mL [1650]). The most commonly reported study drug-related adverse event was grade 1 abdominal discomfort (three [3%] of 100 participants), which was transient. Grade 3 laboratory abnormalities were reported for 21 participants, and two participants had grade 4 laboratory abnormalities (appendix p 8); most were isolated and transient.

Increases from baseline in serum creatinine were observed at week 1 and remained stable through week 48: median change 0·08 mg/dL (IQR 0·03 to 0·14). One patient had a grade 1 increase in serum creatinine. Correspondingly, decreases from baseline in eGFR (Schwartz formula) were observed at week 1, and had stabilised by week 48: median change –16·0 mL/min per 1·73 m² (IQR –33·0 to –1·0); appendix p 10). Minimal changes from baseline were identified in height Z scores and a modest improvement from baseline in weight Z scores (ie, scores were closer to the expected weight for age) at week 48 (appendix p 9).

After switching to bictegravir, emtricitabine, and tenofovir alafenamide, virological suppression (HIV-1 RNA <50 copies per mL) was maintained in all 100 participants at week 24 and 98 (98%) of 100 participants at week 48 (table 4). One participant in cohort 1 had HIV-1 RNA 50 copies per mL or higher at week 48 and one participant in cohort 2 discontinued the study due to an adverse event at week 20, at which time they had virological suppression (HIV-1 RNA <50 copies per mL). Between week 2 and week 48, mean changes from baseline in CD4 count ranged from –40 to 56 cells per µL

	Cohort 1 (age 12 to <18 years; n=50)	Cohort 2 (age 6 to <12 years; n=50)
(Continued from previous page)		
CD4 count category, cells per µL		
<50	0	0
≥50 to <200	0	0
≥200 to <350	2 (4%)	0
≥350 to <500	5 (10%)	2 (4%)
≥500	43 (86%)	48 (96%)
CD4 cell count, %	32·9% (28·5 to 38·2)	36·5% (31·9 to 41·1)
Median time since HIV diagnosis, years (range)	12·0 (3·0 to 17·0)	10·0 (2·0 to 11·0)
Mode of infection (HIV risk factor)‡		
Heterosexual sexual intercourse	1 (2%)	0
Homosexual sexual intercourse	0	0
Intravenous drug use	0	0
Blood transfusion	0	1 (2%)
Vertical transmission	45 (90%)	48 (96%)
Other	0	0
Unknown	4 (8%)	1 (2%)
HIV disease status		
Asymptomatic HIV infection	46 (92%)	47 (94%)
Symptomatic HIV infection	4 (8%)	2 (4%)
AIDS	0	1 (2%)
Antiretroviral regimen before enrolment§		
Multiple tablets	35 (70%)	46 (92%)
Twice daily dosing	24 (48%)	36 (72%)

Data are median (IQR), n (%), or n/N (%), unless stated otherwise. eGFR=estimated glomerular filtration rate. *Some local regulators did not allow collection of race or ethnicity information, or participant's family preferred not to answer; thus, data were missing for one participant in cohort 1. †Maximum stage of pubic hair or genitalia for males, and maximum stage of pubic hair or breasts for females; the denominators are by sex. ‡Participants could be included in more than one HIV risk factor category. §Participants might have been on more than one type of antiretroviral regimen before dosing; therefore, some percentages might sum to more than 100%.

Table 1: **Baseline characteristics**

	Paediatric		Adult*		Geometric least-squares mean ratio of test to reference (90% CI)
	n	Mean (coefficient of variation)	n	Mean (coefficient of variation)	
Cohort 1 (adolescents aged 12 to <18 years with bodyweight ≥35kg)					
Bictegravir†					
AUC_{tau}, ng × h/mL	50	89 100 (31·0%)	1193	102 000 (26·9%)	86·3% (80·0–93·0)
C_{max}, ng/mL	50	6240 (27·1%)	1193	6150 (22·9%)	100% (93·8–107)
C_{tau}, ng/mL	50	1780 (44·4%)	1193	2610 (35·2%)	65·4% (58·3–73·3)
Emtricitabine‡					
AUC_{tau}, ng × h/mL	24	13 600 (21·7%)	77	12 300 (29·2%)	113% (102–124)
C_{max}, ng/mL	24	2690 (34·0%)	77	2130 (34·7%)	127% (111–145)
C_{tau}, ng/mL	24	64·4 (25·0%)	74	96·0 (37·4%)	69·3% (61·6–77·9)
Tenofovir alafenamide†					
AUC_{tau}, ng × h/mL	49	196 (50·3%)	486	142 (17·3%)	128% (116–141)
C_{max}, ng/mL	49	133 (70·2%)	486	121 (15·4%)	88·6% (75·0–105)
Cohort 2 (children aged 6 to <12 years with bodyweight ≥25 kg)					
Bictegravir†					
AUC_{tau}, ng × h/mL	50	128 000 (27·8%)	1193	102 000 (26·9%)	125% (117–134)
C_{max}, ng/mL	50	9460 (24·3%)	1193	6150 (22·9%)	153% (143–163)
C_{tau}, ng/mL	50	2360 (39·0%)	1193	2610 (35·2%)	88·9% (80·6–98·0)
Emtricitabine‡					
AUC_{tau}, ng × h/mL	25	17 600 (36·9%)	77	12 300 (29·2%)	143% (127–159)
C_{max}, ng/mL	25	3890 (31·0%)	77	2130 (34·7%)	185% (162–210)
C_{tau}, ng/mL	24	227 (322·8%)	74	96 (37·4%)	95·0% (69·9–129)
Tenofovir alafenamide†					
AUC_{tau}, ng × h/mL	47	278 (40·3%)	486	142 (17·3%)	183% (165–202)
C_{max}, ng/mL	47	205 (44·6%)	486	121 (15·4%)	153% (136–173)

Data are presented to 3 significant figures. AUC_{tau}=area under the curve at the end of the dosing interval. C_{max}=maximum plasma concentration. C_{tau}=concentrations at the end of the dosing interval. *Pharmacokinetic data obtained for the pooled population from four phase 3 studies[13,14] in adults with HIV (GS-US-380–1489, GS-US-380–1490, GS-US-380–1844, and GS-US-380–1878 for bictegravir), pooled intensive pharmacokinetic data from four phase 3 studies[13,14] in adults with HIV (GS-US-380–1489, GS-US-380–1490, GS-US-380–1844, and GS-US-380–1878 for emtricitabine), and pharmacokinetic data for the pooled population from two phase 3 studies[13,14] in adults with HIV (GS-US-380–1489 and GS-US-380–1490 for tenofovir alafenamide). †Paediatric data were from population pharmacokinetic data. ‡Paediatric data were from intensive pharmacokinetic substudy (part A of the current study).

Table 2: **Summary of pharmacokinetic parameters**

(appendix p 11). At week 48, two participants met criteria for virological resistance testing and no emergence of resistance was identified. Three participants had the emtricitabine-associated resistance mutation Met184Val at baseline and all three maintained virological suppression (HIV-1 RNA <50 copies per mL) at week 48.

Discussion

Week-48 results of this ongoing, single-arm, open-label trial showed that the single-tablet regimen of bictegravir, emtricitabine, and tenofovir alafenamide was well tolerated and highly effective in maintaining virological suppression in adolescents and children with HIV.

Exposure-related adverse events have not been identified in adults receiving bictegravir, emtricitabine, and tenofovir alafenamide using a pharmacokinetic–pharmacodynamic evaluation for the most commonly reported adverse events (unpublished data). The higher exposures of bictegravir C_{max} and tenofovir alafenamide AUC_{tau} and C_{max} observed in children in this study were contained within the range of adult exposures assessed in the pharmacokinetic–pharmacodynamic safety analysis, indicating an absence of clinical impact on safety for these exposures.

Pharmacokinetic parameters are a common primary endpoint in paediatric studies of antiretrovirals. The similarities between disease and antiviral response in children and adults with HIV enable extrapolation of efficacy from adults to children using a pharmacokinetic bridge. If a particular analyte exposure is associated with efficacy in adults, this same efficacy can be extrapolated to a paediatric population if the exposures to the analytes of interest are similar. To assess similarity, GLSM ratios are compared between children and adults using a bioequivalence range. The selection of the bioequivalence range of 70–143% for the GLSM ratio comparison is a generally accepted range used by regulators. Values below this range could potentially suggest reduced efficacy whereas values markedly above this range might affect safety.

Although the reason for the decrease in bictegravir C_{tau} in adolescents relative to the adult mean is unknown, the mean bictegravir C_{tau} (1784 ng/mL) in this study was more than 11-fold higher than the established protein-adjusted 95% effective concentration ($paEC_{95}$) of 162 ng/mL against wild-type virus.[13] This finding, coupled with the high proportion of participants who had virological suppression, indicate that the difference in bictegravir C_{tau} between adults and adolescents is not clinically significant. A modestly higher bictegravir C_{max} (53%) and AUC (25%) in children compared with adults were also not considered clinically important since the observed safety profile in this population was favourable and similar to that observed in the adult population.

Exposures of emtricitabine and tenofovir alafenamide in adolescents and children were within the range of exposures observed from previously published data in adolescents and children for approved emtricitabine and tenofovir alafenamide-containing products, in which there were no associated safety concerns.[29–32]

The safety profile of bictegravir, emtricitabine, and tenofovir alafenamide in adolescents and children was consistent with that observed in adults. One participant in cohort 2 discontinued the study due to grade 2 treatment-related events of insomnia and anxiety. At week 16, the bictegravir trough concentration in this participant was comparable to those of other participants in the same weight band and age cohort. Long-term neuropsychiatric adverse events are being collected for participants remaining in the study extension and new participants with bodyweight 14 kg to less than 25 kg who are receiving a reduced dose with similar bictegravir exposures as the children with a bodyweight of at least 25 kg. No related safety signals have been reported to date.

	Cohort 1 (12 to <18 years; n=50)	Cohort 2 (6 to <12 years; n=50)
Any grade adverse event	40 (80%)	41 (82%)
Any grade adverse event (≥5% in all participants)		
Upper respiratory tract infection	12 (24%)	14 (28%)
Diarrhoea	5 (10%)	6 (12%)
Headache	4 (8%)	5 (10%)
Cough	3 (6%)	6 (12%)
Influenza	6 (12%)	2 (4%)
Nasopharyngitis	3 (6%)	3 (6%)
Respiratory tract infection	3 (6%)	3 (6%)
Vomiting	2 (4%)	4 (8%)
Allergic rhinitis	5 (10%)	1 (2%)
Abdominal pain	3 (6%)	2 (4%)
Streptococcal pharyngitis	0	5 (10%)
Tonsillitis	2 (4%)	3 (6%)
Urinary tract infection	5 (10%)	0
Viral upper respiratory tract infection	4 (8%)	1 (2%)
Decreased appetite	2 (4%)	3 (6%)
Grade 3 or 4 adverse event	3 (6%)	0
Adverse event attributed to study drug*	3 (6%)	8 (16%)
Serious adverse event†	3 (6%)	0
Adverse event leading to study drug discontinuation‡	0	1 (2%)
Death	0	0

Data are n (%). *The most common adverse event attributed to study drug was abdominal discomfort (n=3); all other related adverse events occurred in one participant each. †Grade 2 unrelated abdominal pain (n=1), grade 2 unrelated lung abscess (n=1), and grade 3 unrelated hyperthyroidism (n=1). ‡Grade 2 insomnia and anxiety.

Table 3: **Overall safety summary**

	Cohort 1 (age 12 to <18 years; n=50)	Cohort 2 (age 6 to <12 years; n=50)	Overall (6 to <18 years; n=100)
Week 24	50 (100%; 92·9 to 100·0)	50 (100%; 92·9 to 100·0)	100 (100%; 96·4 to 100·0)
Week 48	49 (98%; 89·4 to 99·9)	49 (98%; 89·4 to 99·9)	98 (98%; 93·0 to 99·8)

Data are n (%; 95% CI).

Table 4: **Virological suppression (HIV-1 RNA <50 copies per mL) at weeks 24 and 48**

Bone density was not measured in this study. No fractures were reported. Additionally, tenofovir exposures in adolescents and children in this study were consistent with tenofovir exposures in children of the same age and bodyweight given coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in whom height-age adjusted BMD Z scores changed minimally from baseline at 24 and 48 weeks.[33] Changes in eGFR were consistent with bictegravir-mediated reduction in activity of the renal transporters, OCT-2 and MATE-1,[29,30] which affect creatinine secretion without affecting actual eGFR.

Weight Z scores, synonymous with the SD of the mean when compared to a reference population of adolescents and children, provides context in regard to individual weight increases or decreases. For the participants of this study, median weight Z scores remained less than zero but improved slightly by 48 weeks. However, median height Z scores showed no change. This observation is consistent with what is commonly observed in virologically suppressed children and adolescents with perinatal HIV infection who have larger improvements in weight than height over time.[31,32]

The favourable safety profile and ease of administration of bictegravir, emtricitabine, and tenofovir alafenamide were reflected in the high levels of adherence and virological suppression at 48 weeks. Moreover, all participants as young as age 6 years found the tablet palatable and acceptable in terms of size and shape. These findings are consistent with the increased adherence associated with single-tablet regimens observed in adults and indicate similar advantages in a population of adolescents and children.[18–21]

Although the specified age range for cohort 2 was 6 years to less than 12 years, dosing predictions for bictegravir, emtricitabine, and tenofovir alafenamide were based on weight rather than age since there is no significant physiological difference in metabolism of these analytes in children of this age group. It was therefore important to ensure enrolment of children with a bodyweight equal to or close to this lower boundary. Thus, two children weighed 25·0 kg at enrolment and four children weighed between 25·0 and 26·0 kg. A low-dose tablet of bictegravir, emtricitabine, and tenofovir alafenamide for children at least 2 years of age and independent of an upper age boundary who weigh less than 25·0 kg is currently being evaluated as part of a separate cohort in this study (NCT02881320).

One potential limitation of our study is the non-comparative design, which was chosen in accordance with regulatory guidance and enabled efficacy to be extrapolated from data in adults.[34–36] This approach expedites drug development for the paediatric population. Although data for 100 participants treated for 6 months are considered sufficient evidence to support the safety of a new antiretroviral for paediatric populations, a 48-week follow-up period with 100 participants would not be adequate to identify rare adverse outcomes.[34]

The bictegravir, emtricitabine, and tenofovir alafenamide patent has been provided to the medicines patent pool to allow generic manufacture. Notably, coadministration with strong cytochrome P450 3A, uridine 5'-diphosphoglucuronosyltransferase 1A1, and P-glycoprotein inducers such as rifampin results in a 75% decrease of bictegravir AUC whereas coadministration with rifabutin results in a 38% reduction.[14] Hence, the efficacy of bictegravir could potentially be compromised in this setting, potentially

restricting its use in children coinfected with tuberculosis. This is a limitation of our analysis and will require further evaluation.

Another potential limitation of our study is that we did not include pregnant individuals. The potential for adolescents to become pregnant while taking the bictegravir, emtricitabine, tenofovir alafenamide single-tablet regimen remains unclear. Outcomes of administration of the bictegravir, emtricitabine, and tenofovir alafenamide fixed-dose tablet to pregnant women continue to be captured in the Antiretroviral Pregnancy Registry (NCT00404989). A study of the pharmacokinetics, safety, and efficacy of bictegravir, emtricitabine and tenofovir alafenamide fixed-dose tablet in virologically suppressed pregnant women with HIV in their second or third trimesters is ongoing (NCT03960645). Additionally, a study to assess pharmacokinetic properties of antiretroviral and anti-tuberculosis drugs, including in adolescents, during pregnancy and postpartum is planned (NCT04518228).

The bictegravir, emtricitabine, and tenofovir alafenamide single-tablet regimen has the potential to meet an unmet need for eligible children and adolescents with HIV. INSTI-based ART is now preferred for children according to paediatric guidelines in the USA and European Union.[1–3] Bictegravir has been shown to have a similar or more favourable resistance profile than dolutegravir, an INSTI frequently recommended in guidelines but with a minimum weight restriction of 40 kg when given as a single-tablet regimen of abacavir and emtricitabine.[5] Bictegravir, emtricitabine, and tenofovir alafenamide has the advantage of providing children and adolescents INSTI-based therapy in the context of a fixed-dose tablet with the well tolerated NRTI backbone of emtricitabine and tenofovir alafenamide. This combination is also currently being studied at reduced doses in a fixed-dose combination in children aged 2 years and older who weigh less than 25 kg, which aligns with the WHO weight band dosing, and will assist in the simplification of drug forecasting for this population.

In summary, in virologically suppressed children and adolescents weighing at least 25 kg, the full-strength formulation of the single-tablet regimen containing bictegravir, emtricitabine, and tenofovir alafenamide was well tolerated and maintained high rates of virological suppression at 48 weeks. No clinically meaningful drug exposure differences relative to adults in phase 3 trials were identified. These results support use of this single-tablet regimen in eligible children and adolescents with HIV, and ongoing paediatric drug development of this treatment regimen at lower doses for younger children.

Contributors

AHG, MFC, CAR, EJM, EH, AL, EN, PK, and KC enrolled participants, reviewed and interpreted analyses of data, and edited or approved the draft manuscript. HMar, HG, and CP designed the study. PW analysed the data, which were reviewed and interpreted by HMax, DP, SM, MSY, HG, HMar, DMB, and CP. PW, SM, MSY, and CP accessed and verified the data. The first draft was written by AHG and CP. All authors contributed to edits of the final manuscript. AHG and CP made the decision to submit the manuscript for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AHG reports that his institution holds a Clinical Trials Agreement with Gilead to support the clinical trials sponsored by Gilead, including those that contributed to data shared in this manuscript; no direct payment was made to AHG. CAR has received research grant support and payment for attending scientific meetings from Gilead. KC reports research support from Gilead. HMax, PW, DP, SM, MSY, HG, HMar, DMB, and CP are or were employees of Gilead at the time of this analysis and report and hold stock interest in the company. All other authors declare no competing interests.

Data sharing

Gilead shares anonymised individual patient data upon request or as required by law or regulation with qualified external researchers. Approval of such requests is at Gilead's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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References

1 Penta Child Health Research. Penta HIV first and second line antiretroviral treatment guidelines 2019. https://penta-id.org/wp/wp-content/uploads/2016/11/PENTA_HIV-1st-2nd-Line-ARV-Treatment-Guidelines-2019_v1.0_20191109.pdf (accessed July 29, 2020).

2 Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf (accessed June 2, 2021).

3 Health and Human Services Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/PediatricGuidelines.pdf (accessed June 2, 2021).

4 Gallant JE, Thompson M, DeJesus E, et al. Antiviral activity, safety, and pharmacokinetics of bictegravir as 10-day monotherapy in HIV-1-infected adults. *J Acquir Immune Defic Syndr* 2017; **75:** 61–66.

5 Tsiang M, Jones GS, Goldsmith J, et al. Antiviral activity of bictegravir (GS-9883), a novel potent HIV-1 integrase strand transfer inhibitor with an improved resistance profile. *Antimicrob Agents Chemother* 2016; **60:** 7086–97.

6 Zhang H, Custodio JM, Wei X, et al. Clinical pharmacology of the HIV integrase strand transfer inhibitor bictegravir. Conference on Retroviruses and Opportunistic Infections; Seattle, WA; Feb 13–16, 2017 (abstr 40).

7 Arribas JR, Thompson M, Sax PE, et al. Brief report: randomized, double-blind comparison of tenofovir alafenamide (TAF) *vs* tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: week 144 results. *J Acquir Immune Defic Syndr* 2017; **75:** 211–18.

8 Gupta SK, Post FA, Arribas JR, et al. Renal safety of tenofovir alafenamide *vs* tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. *AIDS* 2019; **33:** 1455–65.

9 Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2019; **6:** e355–63.

10 Stellbrink H-J, Arribas JR, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2019; **6:** e364–72.

11 Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet* 2017; **390:** 2063–72.

12 Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet* 2017; **390:** 2073–82.

13 BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) [US prescribing information]. Foster City, CA: Gilead Sciences, February, 2018. http://www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.pdf (accessed July 29, 2020).

14 Bictarvy (bictegravir, emtricitabine, and tenofovir alafenamide) summary of product characteristics. Carrigtohill, Ireland: Gilead Sciences Ireland. June, 2019. https://www.ema.europa.eu/en/documents/product-information/biktarvy-epar-product-information_en.pdf (accessed July 29, 2020).

15 European AIDS Clinical Society. Guidelines, version 10.0, November, 2019. https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf (accessed April 29, 2021).

16 Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel. *JAMA* 2018; **320:** 379–96.

17 Penazzato M, Gnanashanmugam D, Rojo P, et al. Optimizing research to speed up availability of pediatric antiretroviral drugs and formulations. *Clin Infect Dis* 2017; **64:** 1597–603.

18 Hines DM, Ding Y, Wade RL, Beaubrun A, Cohen JP. Treatment adherence and persistence among HIV-1 patients newly starting treatment. *Patient Prefer Adherence* 2019; **13:** 1927–39.

19 Schlatter AF, Deathe AR, Vreeman RC. The need for pediatric formulations to treat children with HIV. *AIDS Res Treat* 2016; **2016:** 1654938.

20 Barlow-Mosha LN, Bagenda DS, Mudiope PK, et al. The long-term effectiveness of generic adult fixed-dose combination antiretroviral therapy for HIV-infected Ugandan children. *Afr Health Sci* 2012; **12:** 249–58.

21 Koenig LJ, Lyles C, Smith DK. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis: lessons learned from trials and treatment studies. *Am J Prev Med* 2013; **44** (suppl 2)**:** S91–98.

22 Patel K, Seage GR 3rd, Burchett SK, Hazra R, Van Dyke RB. Disparities in HIV viral suppression among adolescents and young adults by perinatal infection. *Am J Public Health* 2019; **109:** e9.

23 Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. *AIDS Patient Care STDS* 2014; **28:** 128–35.

24 Kim SH, Gerver SM, Fidler S, Ward H. Adherence to antiretroviral therapy in adolescents living with HIV: systematic review and meta-analysis. *AIDS* 2014; **28:** 1945–56.

25 US Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. Corrected Version 2.1. July, 2017. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf (accessed July 29, 2020).

26 Smith F, Hammerstorm T, Soon G, et al. A meta-analysis to assess the FDA DAVP's TLOVR algorithm in HIV submissions. *Drug Inf J* 2011; **45:** 291–300.

27 Sax PE, DeJesus E, Crofoot G, et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. *Lancet HIV* 2017; **4:** e154–60.

28 Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. *CPT Pharmacometrics Syst Pharmacol* 2013; **2:** e38.

29 Zhang H, West SK, Vu A, et al. Lack of clinically relevant effect of bictegravir on metformin pharmacokinetics and pharmacodynamics. International Workshop on Clinical Pharmacology of Antiviral Therapy; Chicago, IL; June 14–17, 2017 (abstr 50).

30 Zhang H, Custodio JM, Wei X, et al. Clinical pharmacology of the unboosted HIV integrase strand transfer inhibitor (INSTI) bictegravir (BIC). Annual Conference of the British HIV Association; Liverpool; April 4–7, 2017 (abstr O2).

31 Mwiru RS, Spiegelman D, Duggan C, et al. Growth among HIV-infected children receiving antiretroviral therapy in Dar es Salaam, Tanzania. *J Trop Pediatr* 2014; **60:** 179–88.

32 Williams PL, Jesson J. Growth and pubertal development in HIV-infected adolescents. *Curr Opin HIV AIDS* 2018; **13:** 179–86.

33 GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) [US prescribing information]. Foster City, CA: Gilead Sciences, December, 2018. https://www.gilead.com/-/media/files/pdfs/medicines/hiv/genvoya/genvoya_pi.pdf (accessed July 29, 2020).

34 US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment. Guidance for industry. November, 2015. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf (accessed Nov 13, 2019).

35 European Medicines Agency. Guideline on the clinical development of medicinal products for the treatment of HIV infection. EMEA/CPMP/EWP/633/02; Rev 3. April 28, 2016. https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-development-medicinal-products-treatment-hiv-infection_en.pdf (accessed Nov 13, 2019).

36 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach-Second edition. June, 2016. http://www.who.int/hiv/pub/arv/arv-2016/en/ (accessed Nov 13, 2019).