Safety, efficacy, and pharmacokinetics of single-tablet elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in virologically suppressed, HIV-infected children: a single-arm, open-label trial

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Summary

Background No once-daily single-tablet regimen is available for HIV-infected children under 12 years. The single-tablet, fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide is a once-daily, integrase strand transfer inhibitor-based regimen approved in the USA and European Union for individuals aged 12 years or older. In this study, we aimed to assess the pharmacokinetics, safety, and efficacy of this regimen in virologically suppressed, HIV-infected children.

Methods In this single-arm, open-label trial, we enrolled virologically suppressed, HIV-infected children from five hospital clinics in Uganda, the USA, and Thailand. Eligible participants were aged 6–11 years, weighed 25 kg or more, had virological suppression (<50 copies of HIV-1 RNA per mL) on a stable regimen for at least 6 months, CD4 count of more than 100 cells per μL, and no history of resistance to elvitegravir, emtricitabine, tenofovir alafenamide, or tenofovir. All participants received the available fixed-dose oral formulation of elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg once per day. Primary outcomes were the pharmacokinetic parameters area under the curve (AUC) concentration at the end of the dosing interval (AUC_{tau}) for elvitegravir and the AUC from time zero to the last quantifiable concentration (AUC_{last}) of tenofovir alafenamide, treatment-emergent serious adverse events, and all treatment-emergent adverse events. Results from baseline to week 24 are reported, unless specified otherwise. Primary and safety analyses included all enrolled participants who received one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01854775.

Findings Between July 27 and Sept 28, 2015, we screened 26 children, of whom 23 were enrolled and initiated treatment. Median age was 10 years (IQR 8–11), median weight was 30·5 kg (IQR 27·5–33·0), and all participants had virological suppression. The mean AUC_{tau} of elvitegravir was 33 814 ng×h/mL (coefficient of variation 58%), and the mean AUC_{last} of tenofovir alafenamide was 333 ng×h/mL (45%). Exposures to elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide were higher, but modestly so, than those previously reported in adults. All 23 participants tolerated the regimen well; there were no serious adverse events or adverse event-related discontinuations. All participants maintained virological suppression (HIV-1 RNA <50 copies per mL) at week 24. CD4 count decreased by a median of –130 cells per μL (range –472 to 266) with little change in CD4 cell percentage (–2·1%, range –8·4 to 5·9).

Interpretation The fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide was efficacious and well tolerated in virologically suppressed, HIV-infected children. Although plasma exposure of all components was higher than has been reported in adults, there were no safety concerns and the overall bone and renal safety profile was favourable. These data support the use of this regimen in children at least 25 kg in weight.

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Introduction

Few antiretroviral, fixed-dose combination options are available for children younger than 12 years, and no once-daily, single-tablet regimens are approved in the USA or the European Union for participants younger than 12 years.[1]

Tenofovir alafenamide, like tenofovir disoproxil fumarate, is an oral prodrug of tenofovir, but tenofovir alafenamide achieves a higher intracellular concentration of tenofovir diphosphate, and approximately 90% lower circulating concentrations of tenofovir.[2] This pharmacokinetic profile, combined with similar efficacy and a more favourable bone and renal safety profile than tenofovir disoproxil fumarate in adults,[3,4] makes tenofovir alafenamide of particular interest for paediatric patients who have not completed peak bone accretion.[5]

The primary consideration in selecting doses of coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in children was to minimise risk of subtherapeutic exposure while simplifying and harmonising weight-based dosing of the single-tablet regimen including the derivative single agents and the

Research in context

Evidence before this study

Although single-tablet regimens improve adherence and ensure target exposures for each component, no once-daily single-tablet regimens are approved for HIV-infected children younger than 12 years. For treatment-naive adults, the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide is one of the guideline-recommended regimens in the USA (Department of Health and Human Services), European Union (European AIDS Clinical Society), and internationally (International AIDS Society). Elvitegravir is an integrase strand transfer inhibitor, which is boosted by cobicistat, a specific and potent CYP3A inhibitor with no anti-HIV activity. In previously published randomised double-blind studies (GS-US-292-0104/0111), tenofovir alafenamide, an oral prodrug of tenofovir, was as efficacious as the other prodrug tenofovir disoproxil fumarate, but had safer bone and renal toxicity profiles, as assessed by estimated glomerular filtration rate, quantitative urinary protein, and bone mineral density.

We searched PubMed using each of the terms "tenofovir alafenamide", "elvitegravir", or "cobicistat", in "children" or "pediatric" or "paediatric" populations, reporting a "trial" or "study". Searches were limited to articles published in English between Jan 1, 1997, and Nov 16, 2016. The search yielded one article, which summarised safety, efficacy, and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in treatment-naive, HIV-infected adolescents (aged 12–18 years) from baseline to week 48. We found no articles for children younger than 12 years.

Added value of this study

To our knowledge, this single-arm, open-label trial is the first to provide the pharmacokinetics, safety, and efficacy data of a single-tablet, fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in HIV-infected, virologically suppressed children younger than 12 years. Other than emtricitabine, none of the other three components of this single-tablet regimen have been assessed in children as individual components or as part of fixed-dose formulations. Although overall drug exposures (area under the curve [AUC]) for each component of the single-tablet regimen were modestly higher in our study population than those in adults, they were not associated with any safety concerns and were within the ranges of AUC observed in clinical studies in adults. Results from this switch study show short-term safety, tolerability, and efficacy of this regimen in children from baseline to 24 weeks: no study drug discontinuations due to adverse events or size or taste of the tablet were reported, total and tubular proteinuria was improved compared with baseline, and positive gains in spine and total body less head bone mineral density and maintenance of virological suppression (<50 copies of HIV-1 RNA per mL) were documented. Although this is a relatively small, non-comparative study of 23 children, it provides important evidence of the safety and antiviral activity of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide for this age group. Such study designs are consistent with and responsive to the European Union and US HIV paediatric regulatory guidance, which allows extrapolation of adult efficacy data.

Implications of all the available evidence

The combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide is a promising once-daily, single-tablet antiretroviral regimen with proven efficacy and safety in some populations, now including virologically suppressed, HIV-infected children (weighing at least 25 kg) who might benefit from the potentially improved bone safety profile of tenofovir alafenamide during a period leading up to peak bone growth. Data from this ongoing study will also support development of other tenofovir alafenamide-containing fixed-dose combination (eg, emtricitabine and tenofovir alafenamide) in similar population or younger age (or lower weight band) children.

fixed-dose combination of emtricitabine and tenofovir alafenamide). This approach is consistent with WHO dosing guidance.[6] The dose selected for assessment in children (same as the adult dose—ie, elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg) was considered appropriate, on the basis of elvitegravir pharmacokinetics in children,[7] similar pharmacokinetic–pharmacodynamics relationships of cobicistat and ritonavir, similar metabolic pathways of tenofovir alafenamide and tenofovir disoproxil fumarate, and tenofovir disoproxil fumarate's dose–exposure relationships.[8] For emtricitabine, the available formulation (oral solution) and dosing recommendation in children (6 mg/kg) are not feasible for fixed-dose combination. Therefore, even though we anticipated higher exposure with the use of the adult dose in children, we selected this dose because the exposure was judged to be within a generally safe range. This is based on WHO dosing recommendations for lamivudine (a compound similar to emtricitabine) in children weighing 25 kg or more, which is the same recommendation as in adults.[6] We also relied on the totality of pharmacokinetic, safety, and efficacy data of coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in adolescents and adults[9–10] to justify the use of the adult dose in children. Additionally, the use of an already-approved adult dose and formulation to do a clinical trial in children was felt to be the most expeditious way to gain paediatric approval.

In this study, we aimed to assess the pharmacokinetics, safety, and efficacy of this formulation in virologically suppressed, HIV-infected children aged 6–11 years.

Methods

Study design and participants

GS-US-292-0106 is an open-label, single-arm, two-part trial done at five hospital clinics in Uganda (one site), the USA (three sites), and Thailand (one site). Intensive pharmacokinetics were assessed in part A of the study but not in part B. Part B was initiated after an independent data monitoring committee reviewed pharmacokinetic and safety data from part A. Here, we describe 24-week data from part A; part B is ongoing.

Eligibility criteria included age 6–11 years, weight at least 25 kg, virological suppression with plasma HIV-1 RNA fewer than 50 copies per mL on a stable regimen for at least 6 months, CD4 count greater than 100 cells per μL, and no history of resistance to elvitegravir, emtricitabine, tenofovir alafenamide, or tenofovir.

This study was approved by local ethics committees. All participants provided written assent, and their parents or caregivers gave written informed consent.

Procedures

Participants received an oral single-tablet coformulation of 150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide once daily with food, throughout the study period. The tablet was capsule shaped (19 mm by 8·5 mm). Post-baseline study visits occurred at weeks 1, 2, 4, 8, 12, 16, and 24 and included clinical and laboratory safety assessments.

Adverse events and laboratory abnormalities were graded according to the Division of AIDS guidelines.[11] Dual-energy radiograph absorptiometry of the spine and total body less head (TBLH) was done at weeks 24 and 48. Laboratory tests of renal tubular proteins (retinol-binding protein and β_2 microglobulin) were done at weeks 8, 12, 24, and 48.

Steady-state plasma concentrations were measured before dosing and at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 5 h, 8 h, and 24 h post dose at the week 4 visit. Plasma concentrations were measured using validated high-performance liquid chromatography–tandem mass spectroscopy (QPS [Newark, DE, USA]).

Plasma HIV-1 RNA (Roche TaqMan 2.0 [Roche Diagnostics, Pleasanton, CA, USA]) was measured at all visits. Virological rebound was defined as having two consecutive visits with HIV-1 RNA at least 50 copies per mL. Participants with an HIV-1 RNA at least 400 copies per mL at their last visit (at or after week 8) also had their virus analysed for the development of resistance.

Adherence was assessed by pill count at each visit except week 2. After the week-24 visit, all participants continued study treatment with visits every 8 weeks to week 48.

Outcomes

The primary endpoints were pharmacokinetic parameters area under the curve (AUC) at the end of the dosing interval (AUC_{tau}) for elvitegravir and AUC from time zero to the last quantifiable concentration (AUC_{last}) for tenofovir alafenamide, and the incidence of treatment-emergent serious adverse events and all treatment-emergent adverse events. The secondary efficacy endpoint was the proportion of participants with HIV-1 RNA fewer than 50 copies per mL at weeks 24 and 48 as defined by the US Food and Drug Administration-defined snapshot algorithm.[12] Other secondary endpoints included additional pharmacokinetic parameters (observed drug concentration at the end of the dosing interval C_{tau}, maximum observed concentration of drug C_{max}, apparent oral clearance after administration of the drug CL/F, and apparent volume of distribution of the drug V_z/F for elvitegravir; C_{max}, apparent CL, and V_z for tenofovir alafenamide; and AUC_{tau}, C_{max}, and C_{tau} for emtricitabine, tenofovir, and cobicistat) and the change from baseline in CD4 cell count and percentage at weeks 24 and 48.

Statistical analysis

A minimum of 18 children were anticipated to provide 92% power to conclude tenofovir alafenamide AUC_{last} equivalence in children versus adults, assuming an expected geometric mean ratio of 1, an equivalency boundary of 70–143%, two one-sided tests with α=0·05, and SD 0·37 ng×h/mL (natural log scale).

Analyses were done after the last participant in part A had completed the week-24 visit and included all enrolled participants who received one dose of study drug. Safety data were summarised using descriptive statistics. Bone mineral density (BMD) height-age *Z* scores were

	Data (n=23)
Age (years)	10 (8–11)
Sex	
Male	9 (39%)
Female	14 (61%)
Country of origin	
Uganda	14 (61%)
USA	6 (26%)
Thailand	3 (13%)
Ethnic origin	
Black	18 (78%)
White	2 (9%)
Asian	3 (13%)
Height (cm)	136·3 (130·5–140·0)
Median height *Z* score	–0·43 (–1·04–0·37)
Weight (kg)	30·5 (27·5–33·0)
Median weight *Z*-score	–0·25 (–1·16 to 0·39)
Estimated glomerular filtration rate (Schwartz formula; mL/min per 1·73 m²)	150·0 (134·7–165·6)
HIV-1 RNA <50 copies per mL	23 (100%)
CD4 count (cells per μL)	969 (843–1087)
HIV infection by vertical transmission	23 (100%)

Data are median (IQR) or n (%).

Table 1: **Baseline characteristics**

	Children (6–12 years)		Adults[102,104,111]*		Geometric least-squares mean ratio of test/reference (90% CI)
	n	Mean (coefficient of variation)	n	Mean (coefficient of variation)	
Elvitegravir					
AUC_{tau}, (ng × h/mL)	22	33 814 (58%)	19	22 797 (35%)	134% (104–173)
C_{max}, (ng/mL)	23	3055 (39%)	19	2113 (34%)	141% (115–173)
C_{tau}, (ng/mL)	23	370 (119%)	19	287 (62%)	86% (55–133)
Cobicistat					
AUC_{tau}, (ng × h/mL)	20	15 891 (52%)	19	9459 (34%)	158% (126–198)
C_{max}, (ng/mL)	23	2079 (47%)	19	1450 (28%)	127% (98–165)
C_{tau}, (ng/mL)	23	96 (169%)	18	21 (85%)	171% (95–310)
Emtricitabine					
AUC_{tau}, (ng × h/mL)	22	20 629 (19%)	19	11 714 (17%)	175% (160–192)
C_{max}, (ng/mL)	23	3397 (27%)	19	2056 (20%)	164% (145–184)
C_{tau}, (ng/mL)	23	115 (24%)	19	95 (47%)	125% (107–146)
Tenofovir alafenamide†					
AUC_{last}, (ng × h/mL)	23	333 (45%)	539	206 (72%)	171% (147–199)
C_{max}, (ng/mL)	23	313 (61%)	539	162 (51%)	182% (146–225)
Tenofovir					
AUC_{tau}, (ng × h/mL)	23	440 (21%)	841	293 (27%)	152% (142–163)
C_{max}, (ng/mL)	23	26 (21%)	841	15 (26%)	173% (161–186)
C_{tau}, (ng/mL)	23	15 (25%)	841	11 (29%)	143% (132–155)

AUC_{tau}=area under the plasma concentration versus time curve over the dosing interval. C_{max}=maximum observed plasma concentration of drug. C_{tau}=observed drug concentration at the end of the dosing interval. AUC_{last}=area under the plasma concentration curve from time zero to the last quantifiable concentration. *Adult pharmacokinetic parameters for elvitegravir, cobicistat, and emtricitabine were derived from intensive pharmacokinetic analysis from Phase 2 study 102; data for tenofovir alafenamide and tenofovir were from population pharmacokinetic analyses in Phase 3 studies 104 and 111. †C_{tau} was not calculated for tenofovir alafenimide due to its short half-life.[12,13]

Table 2: **Summary of pharmacokinetic parameters in children and adults**

generated by substituting height-age for chronological age, where height-age was determined as the age at which a participant's height was the median on the US Centre for Disease Control and Prevention stature-for-age growth charts (boys and girls) for the USA.

Pharmacokinetic parameters were calculated by non-compartmental analysis (WinNonlin software, version 6.3). The linear up/log down trapezoidal rule was used with an extravascular model (oral dosing) with input values for dose, time of dose, plasma concentration, and corresponding real-time values based on drug dosing times. Pharmacokinetic data were summarised using descriptive statistics and compared with historical adult data[10] from two pooled phase 3 studies (tenofovir alafenamide and tenofovir) and a phase 2 study (elvitegravir, cobicistat, and emtricitabine). This study is registered with ClinicalTrials.gov, number NCT01854775.

Role of the funding source

The sponsor had the lead role in study design, data collection, data analysis, data interpretation, and writing of the manuscript. All authors had access to the data and assume responsibility for the integrity and completeness of the data reported. All authors were involved in the development and submission of this manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 27 and Sept 28, 2015, we screened 26 children. Three potential participants did not meet the eligibility criteria, and the remaining 23 participants were enrolled and initiated treatment. Median age was 10 years (IQR 8–11), and median weight was 30·5 kg (27·5–33·0). 14 (61%) of 23 participants were female, and 18 (78%) of 23 participants were black (table 1). At baseline, all participants were asymptomatic and prepubescent (Tanner stages 1–3). Before enrolment, 16 (71%) of 23 participants were taking zidovudine or abacavir as a nucleoside reverse transcriptase inhibitor; two (9%) were on tenofovir disoproxil fumarate. As the third agent, most participants were taking a non-nucleoside reverse transcriptase inhibitor (n=11), followed by a boosted protease inhibitor (n=5), or integrase strand transfer inhibitor (INSTI, n=2).

Between baseline and week 24, no participant discontinued study drug. Median exposure to study drug was 32·1 weeks (IQR 31·7–32·1). Median study drug adherence was 98·1% (94·6–98·8), with 16 (70%) of 23 participants having greater than 95% adherence. 21 (91%) participants reported no issues with the palatability of study drug and product shape or size. One participant reported study drug to be not palatable (product taste abnormal) on day 1 but palatable on day 28. Another participant reported the size to be unacceptable on days 1 and 28. However, both participants continued taking the study drug.

Steady-state pharmacokinetic parameters of individual components are summarised in table 2, along with historical adult data. Exposures of each analyte were generally higher than those in adults.[11,14] Increases in AUC of tenofovir alafenamide (71%), tenofovir (52%), elvitegravir (34%), cobicistat (58%), and emtricitabine (75%) in this paediatric population versus adults were considered modest (table 2). In particular, tenofovir AUC_{tau} (440·2 ng×hr/mL) was approximately five times lower than adult exposures from tenofovir disoproxil fumarate 300 mg (2290 ng×hr/mL).[8] Although slightly lower compared with adults, mean elvitegravir C_{tau} (370 ng/mL) was more than eight times higher than the IC_{95} for wild-type virus (44·5 ng/mL).[7]

The single-tablet regimen was well tolerated, with all adverse events reported as mild or moderate in severity (table 3). No participant died or had adverse events leading to study drug discontinuation or serious adverse events. Abdominal pain and vomiting were the most commonly reported study drug-related adverse events (four of 23 participants), and were transient and grade 1–2.

No fractures or cases of Fanconi syndrome or proximal renal tubulopathy occurred. Grade 3 laboratory abnormalities were reported in five participants (four neutropenia, one hypocalcemia, one hypomagnesemia, and one hematuria) and most were isolated and transient. The grade 3 neutropenia normalised or returned to baseline when continuing study drug in all four participants, and none of these participants had adverse events as a result of neutropenia. No grade 4 laboratory abnormalities were reported.

Median baseline serum creatinine was 0·52 mg/dL (IQR 0·45–0·55). Increases were seen at week 4 that remained stable from baseline to week 24 (median change 0·04 mg/dL [0·01–0·07]). No graded abnormalities in serum creatinine were reported. Median estimated glomerular filtration rate using the Schwartz formula was 150·0 mL/min per 1·73 m² (134·7–165·6) at baseline and decreased at week 4 (–9·9 mL/min per 1·73 m², –18·9 to 4·3) and week 24 (–6·5 mL/min per 1·73 m², –18·7 to 5·9).

At baseline, one (4%) of 23 participants had grade 1 proteinuria as assessed by dipstick analysis. Post-baseline, treatment-emergent, isolated, and transient grade 1 proteinuria was reported in three (13%) of 23 participants, who did not have any other renal abnormalities. Quantitative measures of total and tubular proteinuria improved (table 4). Median percentage change in urine protein to creatinine ratio from baseline at week 24 was –30·3% (IQR –54·1 to 23·8). Median percentage change in urine β_2-microglobulin to creatinine ratio was –6·2% (–35·1 to 35·2) and in urine retinol binding protein to creatinine ratio was –31·1% (–42·3 to 21·5). Median serum phosphorous values were within normal ranges throughout the study, and no graded abnormalities in urine glucose were reported.

Spine and TBLH BMD increased as expected in growing children. Median change in spine BMD was 4·15% (IQR –2·42 to 7·25) and that of TBLH BMD was 1·16% (0% to 3·76) at week 24 (table 4). Importantly, no notable changes in BMD height-age *Z*-scores were seen; median change in spine BMD height-age *Z*-score was 0·10 (–0·29 to 0·48) and in TBLH height-age *Z*-score was –0·12 (–0·25 to –0·02). At week 24, two participants had a 4% or larger decrease in spine BMD and none had a 4% or larger decrease in TBLH BMD. Bone turnover markers increased over 24 weeks (appendix).

After the switch to elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide, virological suppression (HIV-1 RNA <50 copies per mL) was maintained in all 23 participants at week 24. Median CD4 count was 969 cells per µL (range 603 to 1421) at baseline, with change at week 24 of –130 cells per µL (range –472 to 266). For 19 participants who reached week 32, median CD4 count had returned to near baseline value (849 cells per µL, range 545 to 1433). Additionally, median change from baseline in CD4 cell percentage at week 24 was minimal (–2·1%, range –8·4% to 5·9). From baseline to week 24, no participant met criteria for virological resistance testing.

	Data (n=23)
Patients reporting adverse events	
Any adverse event	17 (74%)
Any grade 3 or greater adverse event	0
Any adverse event assessed as related to treatment	9 (39%)
Any grade 3 or 4 adverse event assessed as related to treatment	0
Any serious adverse event	0
Any serious adverse event assessed as related to treatment	0
Any adverse event leading to premature discontinuation of treatment	0
Death	0
Patients reporting study drug-related adverse events	
Abdominal pain	4 (17%)
Vomiting	4 (17%)
Constipation	1 (4%)
Vitamin D deficiency	1 (4%)
Dizziness	1 (4%)
Headache	1 (4%)
Product shape issue	1 (4%)
Product size issue	1 (4%)

Data are n (%).

***Table 3*: Adverse events**

Discussion

Results of this ongoing, single-arm, open-label trial at week 24 show that the single-tablet fixed-dose combination regimen of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide was well tolerated and efficacious in maintaining virological suppression in HIV-1-infected children weighing at least 25 kg, with no new clinically relevant safety findings. Importantly, tenofovir alafenamide was associated with minimal short-term adverse renal and bone effects, which are consistent with findings in adults and adolescents.[3,9] Minimising bone and renal toxicity is of particular importance for children.[14] Tenofovir alafenamide has less bone and renal toxicity than tenofovir disoproxil fumarate, most probably because of lower plasma tenofovir exposure, which is a proxy of bone and renal tissue concentrations.[3,4]

Decreases in total urinary protein and tubular proteins such as retinol binding protein and β_2-microglobulin are consistent with observations in adults. This suggests a lack of adverse renal effect of tenofovir alafenamide. Changes in estimated glomerular filtration rate were consistent with the inhibitory effect of cobicistat on tubular secretion of creatinine, which does not affect actual glomerular filtration rate.[15]

The absence of notable changes in height-age-adjusted spine and TBLH BMD *Z*-scores at week 24 indicates that participants mineralised bone at rates consistent

See Online for appendix

	Baseline	Week 24	Actual or percentage change from baseline at week 24
Estimated glomerular filtration rate (Schwartz formula; mL/min per 1·73 m²)	150·0 (134·7 to 165·6)	143·7 (121·8 to 161·4)	−6·5 (−18·7 to 5·9)
Urine protein to creatinine ratio (mg/g)	87·7 (57·8 to 162·5)	69·6 (51·7 to 86·7)	−30·3% (−54·1 to 23·8%)
Urine β_2 microglobulin to creatinine ratio (µg/g)	124·1 (93·0 to 210·1)	106·6 (81·8 to 155·3)	−6·2% (−35·1 to 35·2%)
Urine retinol binding protein to creatinine ratio (µg/g)	102·9 (68·5 to 123·9)	58·1 (47·8 to 91·2)	−31·1% (-42·3 to 21·5%)
Spine BMD (g/cm²)	0·58 (0·53 to 0·66)	0·59 (0·54 to 0·70)	4·15% (−2·42 to 7·25%)
TBLH BMD (g/cm²)	0·66 (0·64 to 0·71)	0·68 (0·66 to 0·71)	1·16% (0·00 to 3·76%)
Spine BMD height-age *Z*-score	−0·81 (−1·07 to −0·28)	−0·45 (−1·26 to −0·07)	0·10 (−0·29 to 0·48)
TBLH BMD height-age *Z*-score	−0·83 (−1·17 to −0·32)	−0·88 (−1·54 to −0·53)	−0·12 (−0·25 to −0·02)

Data are median (IQR). BMD=bone mineral density. TBLH=total body less head.

Table 4: **Renal and bone safety parameters**

with the reference population. Few participants had clinically relevant decreases in BMD, and most had BMD *Z*-scores consistent with other studies of HIV-infected children.[16,17] By contrast, in a study investigating tenofovir disoproxil fumarate versus a first-line antiretroviral therapy without tenofovir disoproxil fumarate in children 3–18 years of age (median age 12·2 years), three (8%) of 39 children had a decrease in spine BMD *Z*-scores to less than −2·0 at week 24.[18] Thus, tenofovir alafenamide-containing regimens appear to have little to no effect on bone mineralisation in a population approaching the pubertal growth spurt. Increases in bone turnover markers in our study probably represent skeletal growth in children rather than bone toxicity of tenofovir alafenamide,[19] in view of the overall favourable bone safety data of tenofovir alafenamide in treatment-naive and virologically suppressed adults.[3,20]

We observed a small decline in CD4 cell count at week 2 that did not progress further and returned to near baseline by week 32. Since changes in CD4 cell percentage were minimal, these changes in CD4 cell count do not appear clinically relevant and might have been driven by variability in the small number of participants.

The increase in AUC values of each component of the fixed-dose combination in our study population compared with historical adult data were considered modest when taking into consideration their observed variability in adults. Importantly, the ranges of AUC values for all components in our study population were within those observed in clinical studies in adults (including those with estimated glomerular filtration rate >30 mL/min per 1·73 m², in whom no corresponding safety signals exist).[3,15,20] Additionally, considering that tenofovir exposures are the most relevant parameter in assessing the safety of tenofovir alafenamide relative to tenofovir disoproxil fumarate, children taking this fixed-dose combination still had five times lower tenofovir exposures than did adults on regimens containing tenofovir disoproxil fumarate.

Almost all participants found the tablet palatable and acceptable in terms of size and shape. Children are usually able to swallow tablets at 6 years of age, although some as young as 3–4 years of age can do so with proper motivation or training.[21–23] Once-daily regimens are associated with high adherence.[24,25] These advantages of single-tablet regimens are leading some paediatricians to prescribe adult single-tablet regimens to children weighing as little as 10 kg in resource-limited settings.[26]

Our study has a non-comparative design with a small sample size of mostly black participants. However, as per regulatory guidance, demonstration of efficacy in paediatric participants by use of large randomised clinical trials is not required because efficacy can be extrapolated from adult data.[27,28] This approach expedites drug development for paediatric populations. Although the non-comparative design is not scientifically ideal, availability of adult data from several randomised controlled trials, which consistently showed the safety benefit of tenofovir alafenamide (*vs* tenofovir disoproxil fumarate), should be taken into account when interpreting safety results from our study. Given the small sample size, we are enrolling additional children as per the protocol to participate without undergoing intensive pharmacokinetic assessment. All participants will continue to be followed up to assess longer-term efficacy and safety up to 48 weeks. The assessment of longer-term renal and bone safety will be particularly important in the context of higher exposures of tenofovir alafenamide and tenofovir in children than in adults. Probably because of the weight cutoff (ie, 25 kg or more), no participants were 6–7 years of age. However, this might be less relevant as drug exposures depend on weight in this age group.[29] The predominance of black participants simply reflects racial and geographical disparity of paediatric HIV infection.

The fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in HIV-1 infected children has the potential to fill an unmet medical need. First, the once-daily tablet will be a convenient regimen to simplify antiretroviral therapy

administration.[21] Second, tenofovir alafenamide will be a potent, safe, and well tolerated nucleoside reverse transcriptase inhibitor alternative in this population compared with tenofovir disoproxil fumarate and other paediatric guideline-recommended nucleoside reverse transcriptase inhibitor agents, such as abacavir or zidovudine. Third, this single-tablet regimen brings to children the benefit of the INSTI class, such as potency, safety, and tolerability—advantages that have placed INSTI-based regimens as the most commonly recommended in treatment guidelines.[29] In the future for children weighing less than 25 kg, a tenofovir alafenamide-based regimen will be studied using coformulated emtricitabine and tenofovir alafenamide, or coformulated bictegravir, emtricitabine, and tenofovir alafenamide, the latter coformulation being a new INSTI-based, tenofovir alafenamide-containing single-tablet regimen in development.[30]

In summary, in virologically suppressed children weighing at least 25 kg, a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide was well tolerated and maintained high virological suppression from baseline to 24 weeks. These results, combined with the favourable bone and renal safety profile of tenofovir alafenamide, support use of this single-tablet regimen in HIV-1 infected children.

Contributors

All authors were involved in the development of this manuscript, interpretation of data, have read and approved the final version, and have met the criteria for authorship as established by the ICMJE. EN and AHG enrolled participants, analysed data, and independently interpreted the results, and edited and approved the manuscript. PK, JB, and NR enrolled participants, reviewed and interpreted analyses of data, and edited the draft report. DP, MSR, and YS, designed the study. YS and DP did the data analyses, which were reviewed and interpreted by HZ, CP and MSR. The first draft was written by EN, AHG, and MSR. All authors contributed to edits of the submitted manuscript.

Declaration of interests

AHG declares grants from Gilead during the conduct of the study and outside the submitted work. PK reports receiving grants from Khon Kaen University. DP, YS, HZ, and MSR are employees of Gilead and hold stock interest in the company. All other authors declare no competing interests.

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