HHS Public Access

Author manuscript

Pediatr Infect Dis J. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Pediatr Infect Dis J. 2015 November ; 34(11): 1207–1213. doi:10.1097/INF.0000000000000848.

Safety, Pharmacokinetics and Efficacy of Dolutegravir in Treatment-Experienced HIV-1 Infected Adolescents: 48-Week Results from IMPAACT P1093

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Abstract

Objective—To assess the pharmacokinetic (PK), safety and efficacy of dolutegravir plus optimized background regimen (OBR) in HIV infected treatment-experienced adolescents.

Methods—Children ≥12 to < 18 years received dolutegravir weight-based fixed doses at ~1.0 mg/kg once daily in a Phase I/II multicenter open-label 48 week study. Intensive PK evaluation was done at steady state after dolutegravir was added to a failing regimen or started at the end of a treatment interruption. Safety and HIV RNA and CD4 cell count assessments were performed through Week 48.

Results—Twenty three adolescents, were enrolled and 22 (96%) completed the 48 week study visit. Median age and weight were 15 years and 52 kg, respectively. Median (IQR) baseline CD4+ cell count was 466 cells/μL (297, 771). Median (IQR) baseline HIV-1 RNA $\log_{10}$ was 4.3 $\log_{10}$ copies/mL (3.9, 4.6). Dolutegravir geometric mean $AUC_{(0–24)}$ and C_{24} were 46.0 μg.h/mL and 0.90 μg/mL, respectively, which were within the study targets based on adult PK ranges. Virologic success with an HIV RNA < 400 copies/mL was achieved in 74 % (95% CI: 52% to 90%) at Week 48. Additionally, 61% (95% CI: 39% to 80%) had an HIV RNA < 50 copies/mL at Week

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Disclosures: The authors have no conflict of interest or funding to disclose, except for Debra Steimers and Sherene Min who are GSK employees and own stock and/or stock options in the company.

Presented in part at the Conference on Retroviruses and Opportunistic Infections, CROI 2014, March 4rd 2014, Boston, MA. Poster # 906LB.

48. Median (IQR) gain in CD4 cell count at Week 48 was 84 cells/μL (−81, 238). Dolutegravir was well tolerated, with no Grade 4 AEs, SAEs or discontinuations due to AEs.

Conclusions—Dolutegravir achieved target PK exposures in adolescents. Dolutegravir was safe and well tolerated, providing good virologic efficacy through Week 48.

Keywords

Antiretroviral agents; Dolutegravir; HIV integrase inhibitors; Pediatric HIV; Adolescent HIV

Effective combination antiretroviral therapy for HIV treatment results in a reduction in viral load with a concomitant increase in the CD4 cell count and has been associated with declining morbidity, hospitalizations and mortality in HIV-1 infected children [1–5]. However, incomplete adherence, short and long-term toxicities and lack of treatment alternatives further complicate HIV management and may contribute to the development of drug resistance mutations [6, 7]. Therefore, children and adolescents who have manifested multiple class intolerance and/or harbor drug-resistant virus have an unmet medical need. The development of drugs that block alternative or novel targets in the HIV life cycle are critically important for children and adolescents who have failed or are unable to tolerate currently available antiretrovirals. In addition, newer agents with novel resistance patterns not overlapping with established classes of therapies are also needed.

Integrase, a viral enzyme essential for HIV-1 replication, mediates the integration of the viral DNA into the host genome. Three integrase inhibitors have been approved by the Food and Drug Administration FDA. Raltegravir was the first FDA and European Medicines Agency (EMA) approved HIV integrase strand transfer inhibitor and has demonstrated safety and efficacy in both treatment-naïve and highly antiretroviral (ARV) experienced adults [8, 9]. In addition, raltegravir has demonstrated safety and efficacy in treatment experienced children and is FDA approved for children > 4 weeks of age. [10, 11]. A second integrase inhibitor, elvitegravir has also shown safety, potent antiviral activity and efficacy in Phase III clinical trials in adults and recently received FDA approval for ARV naïve adults as a co-formulated pill which includes tenofovir DF, emtricitabine, and cobicistat [12, 13]. However, raltegravir needs to be administered twice a day and has wide inter- and intra-subject pharmacokinetic (PK) variability, while elvitegravir, administered once a day, requires a pharmacoenhancer. In addition, clinical resistance to both raltegravir and elvitegravir has been reported with both agents sharing similar mutation pathways [14, 15].

Dolutegravir (GSK1349572) is a potent inhibitor of the HIV-1 integrase that has shown good safety, tolerability, predictable PK and efficacy in treatment naïve and experienced adults in Phase III trials [16–18]. Dolutegravir is now FDA and EMA approved for both adults and adolescents 12 years and older, weighing ≥ 40 kg, at a dose of 50 mg once a day based in part on the data reported herein [16, 17, 19, 20]. The objective of the IMPAACT P1093 study is to evaluate the safety, tolerability, PK and antiviral efficacy of dolutegravir in combination with an optimized background regimen in HIV infected, treatment experienced adolescents and children, 4 weeks to 18 years of age. Here we report on the results of the adolescent cohort of P1093.

METHODS

Study design and participants

P1093 is an open label, non-randomized, multicenter Phase I/II study of HIV infected, treatment experienced children between 4 weeks and <18 years in age defined cohorts. Children and adolescents between 12 years and <18 years old constitute Cohort I and are the subject of this report. Entry criteria included plasma HIV RNA >1,000 copies/mL, being ART-experienced but naïve to integrase inhibitors, having a screening HIV genotype showing sensitivity to at least one other active antiretroviral agent, laboratory values < Grade 2 toxicity criteria, and absence of active opportunistic infection or current cancer. The study was conducted at the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network sites, after approvals were obtained from local Institutional Review Boards (IRBs) and in-country Ethics Committees (ECs) responsible for oversight of the study. All parents, legal guardians and study participants gave written informed consent. Children were informed about the study and gave assent.

The study was conducted in 2 stages. Stage I evaluated intensive PK, short and long term safety. Dolutegravir dose was prescribed using the weight band approach as follows: 50 mg for children ≥ 40 kg, 35 mg for children between 30 and 40 kg and was available as 50 mg, 25 mg and 10 mg tablets. Dolutegravir was added to a stable, failing regimen (defined as no change in ARV therapy for ≥12 weeks); for this stage, the ARV background of the failing regimen could not include an NNRTI, boosted tipranavir, fosamprenavir or atazanavir due to concerns about PK interactions. The intensive PK sampling was performed between days 5–10, followed by implementation of an optimized background regimen that was chosen by the clinician with approval of the study chairs. Alternatively, subjects who were treatment experienced but off treatment for ≥4 weeks prior to study entry were treated with dolutegravir monotherapy with a new optimized background regimen (OBR) added to dolutegravir after completion of intensive PK sampling (on days 5–10; Figure 1).

Additional participants were enrolled into Stage II which assessed long term safety and efficacy when treated with the Stage I dolutegravir selected dose. For subjects enrolling in Stage II, dolutegravir was initiated concurrently with the chosen OBR (Figure 1). Based upon the findings in Stage I, the chosen dolutegravir dose was approximately 1 mg/kg once a day (QD), with a maximum daily dose of 50 mg, which is the FDA approved dose based on data from Phase III studies in HIV infected, INI-naive adults [16, 21]. For Stage I, the dose finding algorithm for each cohort includes a review of Week 4 safety and intensive PK data in the first 4 subjects (termed a “mini-cohort”) enrolled. If these pre-determined safety and PK criteria were met, accrual to enroll a total of 10 evaluable participants into Stage I ensued. Stage I success, for safety, was defined as: 1) no life-threatening suspected adverse drug reaction [SADR]; 2) no Grade 4 event considered probably or definitely attributable to dolutegravir; and 3) no more than 25% terminating study treatment due to a Grade 3 SADR.

The PK objective was to achieve a concentration-time profile similar to that attained in adults at the approved dolutegravir dose of 50 mg QD. The specific PK targets included geometric mean (GM) of the area under the plasma concentration time curve from time of administration to 24 hours after dosing ($AUC_{0–24hr}$) between 37–67μg.h/mL and a GM 24

hour post-dose concentration (C_{24hr}) of 0.77–2.26 μg/mL; the lower end of these targets represent 80% of the geometric means achieved in adults while the upper limits are at the 90th percentile seen in adults.

After entry and intensive PK evaluations (Stage I only), all participants were evaluated at weeks 4, 8, 12, 16, 24, 32, 40 and 48. Sites were required to report all grade ≥3 toxicity events, serious adverse events (SAE), malignancies and pregnancies to the P1093 team and study sponsor; NIAID Division of AIDS. All subjects completed an adherence questionnaire and site personnel collected and counted the returned dolutegravir tablets to determine missed doses. Plasma HIV RNA concentrations were determined at entry and at regular intervals using the RealTime HIV-1 (Abbott Molecular). Virologic failure was defined as a confirmed decrease in HIV RNA of < 1.0 $\log_{10}$ at or after week 12 or a confirmed HIV RNA > 400 copies/mL at week 24 and beyond on 2 consecutive measurements. Emergence of resistant virus was monitored by isolating viral RNA from all subjects displaying virologic failure, by performing genotypic assays for protease and reverse transcriptase resistance using the TRUGENE® HIV-1 Genotyping Assay (SIEMENS), following the manufacturer's instructions. Integrase inhibitor genotypic resistance was evaluated simultaneously with baseline and virologic failure samples using the HIV-1 integrase resistance genotype assay developed and validated by the University of North Carolina Center for AIDS Research Virology Core Laboratory.

Bioanalysis and Pharmacokinetics

Dolutegravir plasma concentrations were quantified using liquid chromatography with tandem mass spectrometry as previously described [22]. Whole blood was collected at time 0 (pre-dose) and at 1, 2, 3, 4, 6, 8 and 24 hours post dosing. Dolutegravir steady-state pharmacokinetic parameters; area-under-the-curve ($AUC_{0–24}$), plasma concentration observed at the end of 24 hour (C_{24}) were calculated using Phoenix WinNonlin version 6.3 (Certara USA, Inc., St. Louis, MO) and were performed in real-time at the IMPAACT Pharmacology Support Laboratory at the University of Alabama at Birmingham.

Statistics

The primary analysis in stage I was to evaluate the steady state PK of dolutegravir in treatment-experienced HIV-1 infected adolescents and to determine the dose of dolutegravir that achieves a targeted AUC_{24} (primary PK endpoint) and C_{24h} (secondary PK endpoint) in this population. The safety and efficacy analysis was conducted in subjects treated with the selected dose of dolutegravir, whether enrolled in Stage I or II and who completed 48 weeks. Efficacy responses were secondary objectives, and response at Week 48 was assessed with the Snapshot algorithm defined by the US FDA [23]. Virologic success, was defined as achieving a plasma HIV-1 RNA < 400 copies/mL at Week 48. Other secondary efficacy objectives included the proportion achieving HIV-1 RNA < 50 copies/mL, and the change from baseline in CD4 cell count and percentage at Week 48. For virologic endpoints, missing values were considered as failures, if missing due to discontinuation of study treatment for lack of efficacy or for non-treatment related reasons with the last available HIV-1 RNA value not achieving virologic success. For change from baseline in CD4 cell

count and percentage, baseline values were carried forward for missing data as described above.

RESULTS

Baseline characteristics

Twenty three adolescents (Stage I, n=10; Stage II, n=13) were enrolled between April 2011 and April 2012, and 22 (96%) completed the 48 week study visit. One subject discontinued the study drug at Week 40 due to non-compliance. Most subjects were female (78%), with a broad representation of ethnicity, a median age (range) of 15 years (12, 17) and median (range) weight of 52 kg (33, 91). All 23 subjects were NRTI experienced, the majority were PI and NNRTI experienced and 35% were triple class experienced. In addition, 2/23 (9%) were entry inhibitor (enfuvirtide) experienced. The median (IQR) exposure to antiretrovirals was 12.5 years (10.8, 14.0; Table 1). In Stage I, 4/10 subjects were on a PI based failing regimen which included either stavudine or zidovudine (ZDV) and lamivudine (3TC) or emtricitabine (FTC) and nelfinavir or lopinavir/ritonavir (LPV/r). Five subjects had discontinued a PI failing regimen, either atazanavir (ATV)/r or LPV/r prior to enrolment and one discontinued an NRTI based regimen. In Stage II 11/13 subjects were on a failing regimen, 7 on a PI based regimen mostly on ATV/r or LPV/r and 4 were on an NNRTI based regimen, mostly nevirapine (NVP) and 2/13 subjects had discontinued a PI based ART (ATV/r or LPV/r) prior to enrollment.

Optimized Background Regimen

The most common optimized background regimen (OBR) was tenofovir DF (TDF), FTC, darunavir/ritonavir (DRV/r) in 7/23 (30%), abacavir (ABC), 3TC, DRV/r in 3/23 (13%), TDF, 3TC, LPV/r, in 3/23 (13%), TDF, FTC, efavirenz (EFV) in 3/23 (13%) and TDF, FTC in 2/23 (9%), The median (range) weighted genotypic sensitivity score of these regimens was 2.5 (2, 3.5; Table 1).

Intensive Pharmacokinetics

During Stage I, 9 subjects received dolutegravir 50mg and 1 subject received dolutegravir 35mg daily. The dolutegravir dosage of approximately 1 mg/kg/day achieved the desired primary endpoint ($AUC_{0–24}$) and secondary endpoint (C_{24}) with no dose adjustment or modification (Table 2). Dolutegravir demonstrated moderate inter-subject PK variability; geometric mean (CV%) $AUC_{0–24}$ and C_{24} were 46.0 (43%) μg.h/mL and 0.90 (58%) μg/mL, respectively (Table 2).

Safety and Adverse Events

Dolutegravir was well tolerated with all subjects experiencing at least one Grade 1 or 2 transient clinical events. Most frequent reported events were as follows: gastrointestinal; diarrhea in 8 (35%), decrease appetite in 7 (30%), abdominal pain in 5 (21%) and nausea in 3 (13%).Respiratory; cough in 13 (56%), pharyngeal pain in 8 (35%), nasal congestion in 7 (30%) and sinus congestion in 4 (17%). Musculoskeletal; extremity pain in 6 (26%), arthralgia in 3 (13%) and back pain in 3 (13%). General; fever in 7 (30%), lymphadenopathy in 6 (26%), headache in 6 (26%) and dizziness in 4 (17%). None of which were considered

related to dolutegravir and are common events among adolescents with intercurrent illnesses. There were 2 Grade 3 clinical events: gastritis and deep vein thrombosis, not considered related to dolutegravir that resolved without dolutegravir discontinuation. Two subjects experienced Grade 3 laboratory abnormalities; one developed unconjugated bilirubin elevation while on atazanavir as part of the OBR. Another subject developed transient asymptomatic lipase elevation, which was deemed treatment unrelated. There were no Grade 4 AEs, SAEs or discontinuations due to AEs.

Efficacy

The proportion of patients with plasma HIV RNA less than 400 copies/mL and less than 50 copies/mL increased sharply from baseline to week 4, then it generally remained stable through week 48 (Figure 3a and 3b). Virologic success, was achieved in 17/23 subjects (74%; 95% CI: 52% to 90%) at Week 48. Additionally, 14/23 (61%; 95% CI: 39% to 80%) had an HIV RNA load < 50 copies/mL at Week 48. Median (IQR) gain in CD4 cell count and % at Week 48 was 84 cells/μL (−81, 238) and 4.7% (0, 9.4) respectively (Figure 2a and 2b).

Antiretroviral Drug Resistance

There were 6 subjects (26%) who experienced virologic failure on or before Week 48. All 6 subjects had samples analyzed for genotypic resistance. One of these subjects had a treatment-emergent R263R/K at the failure time point. There was no corresponding dolutegravir phenotypic data at the failure time point to assess dolutegravir susceptibility in the presence of this INI mutation. Baseline and virologic failure genotypic resistance mutations are shown in Table 3.

Adherence

Overall 12/23 (52%) of treated patients reported 100% adherence, while 5/23 (22%) were 90% –99% adherent, 2/23 (9%) were 80% –89% adherent, 3/23 (13%) were 70% –79% adherent and 1/23 (4%) was < 70% adherent. All participants with 90% or higher adherence had a VL < 400 copies/mL at Week 48.

DISCUSSION

This study shows that dolutegravir treatment in adolescents 12 to <18 years old using a weight band approach with a dose of approximately 1 mg/kg/day, results in a pharmacokinetic profile comparable to the target AUC_{24} and C_{24} achieved in adults treated with a dose of 50 mg once a day [16, 21]. In addition, dolutegravir was well tolerated when used as a component of an optimized background regimen in treatment experienced adolescents with no Grade 3 or 4 clinical events and no toxicity related treatment discontinuation seen in the 48 week analysis. Dolutegravir appears to have a good safety profile in adolescents when compared to the latest FDA approved protease inhibitors tipranavir and darunavir [24, 25]. In the pediatric tipranavir study, 25% of treatment experienced children reported serious adverse events leading to treatment discontinuation in 8% compared to none of the children in our dolutegravir study [24]. In the darunavir study serious adverse events were less frequent (14%) than in the tipranavir study, leading to

treatment discontinuation in 1%, although treatment discontinuation was not related to darunavir [25]. Raltegravir, another integrase inhibitor, was studied in an adolescent population enrolled in IMPAACT P1066 which had a very similar design to P1093, with participants having a favorable safety profile in children, supporting the use of integrase inhibitors in pediatric populations [10].

Our study found that dolutegravir combined with an optimized background regimen in treatment experienced adolescents has a similarly fast viral decay [21] and an efficacy profile comparable to adults, with 74% of participants achieving an HIV RNA load of < 400 copies/mL at 48 weeks, and with 61% reaching an HIV RNA level of < 50 copies/mL at 48 weeks. In a phase III antiretroviral experienced, integrase-inhibitor-naïve adult population, the efficacy of dolutegravir at 48 weeks measured as an HIV RNA < 50 copies/mL was 71%, slightly better than the 61% found in our adolescent study. Given the median age of 42 years in the adult study and the median age in our study (15 years), this finding is not surprising given the poor adherence characterizing the adolescent population [18] [26]. All of the P1093 study participants with >90% adherence had VL <400 copies/mL at week 48 demonstrating the potency of this treatment class and the real-life challenges of adherence to antiretrovirals in adolescents. The virologic efficacy profile of dolutegravir in adolescents was comparable to the results of raltegravir, using a similar study design [10]. In the raltegravir study, the virologic efficacy of the adolescent cohort at week 48 was 57%, slightly lower than our study.

The 6 participants experiencing virologic failure (VL> 400 copies/mL) in the 48 week analysis had suboptimal adherence, and all had similar baseline and a virologic failure HIV drug resistance genotype. One of these six subjects developed a R263R/K at virologic failure. This non polymorphic INI associated mutation was identified during in-vitro passage [27, 28] and was seen in 2 patients while on dolutegravir treatment, experiencing virologic failure in an ART experienced adult study [18]. In-vitro studies showed a low dolutegravir Fold-Change (FC) in virus harboring the R263K and in the adult study where this mutation was seen, dolutegravir FC values at virologic failure were <2 fold. [29].

Based on the results of several Phase III trials in treatment naïve and experienced adults [16, 17] and the results of the Phase I/II IMPAACT P1093 study in treatment experienced adolescents reported here [19, 20], the U.S. FDA, EMA, and other regulatory agencies globally granted approval to dolutegravir for use in treatment naïve and experienced individuals older than 12 years of age weighing at least 40 Kg; the first time that an antiretroviral has received approval in adults and adolescents simultaneously. Drug development for HIV infected children has lagged behind the adult regulatory approvals since the early stages of the HIV epidemic in part due to the many challenges of pediatric drug development [30]. The rapid development of the pediatric Phase I/II study of dolutegravir was based on a close collaboration between academia through the NIH funded IMPAACT Network and industry (ViiV Healthcare and GlaxoSmithKline) early on in the dolutegravir development program.

Our study results shows that the second generation integrase inhibitor dolutegravir administered once a day represents a new safe and effective treatment option, in conjunction with OBR, in HIV infected treatment experienced adolescents.

ACKNOWLEDGEMENT

We thank all the patients and their caregivers participating in the P1093 study.

Source of Funding: Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Additional funding support was provided by ViiV Healthcare. Clinical trial.gov registration identifier: NCT01302847

Appendix

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

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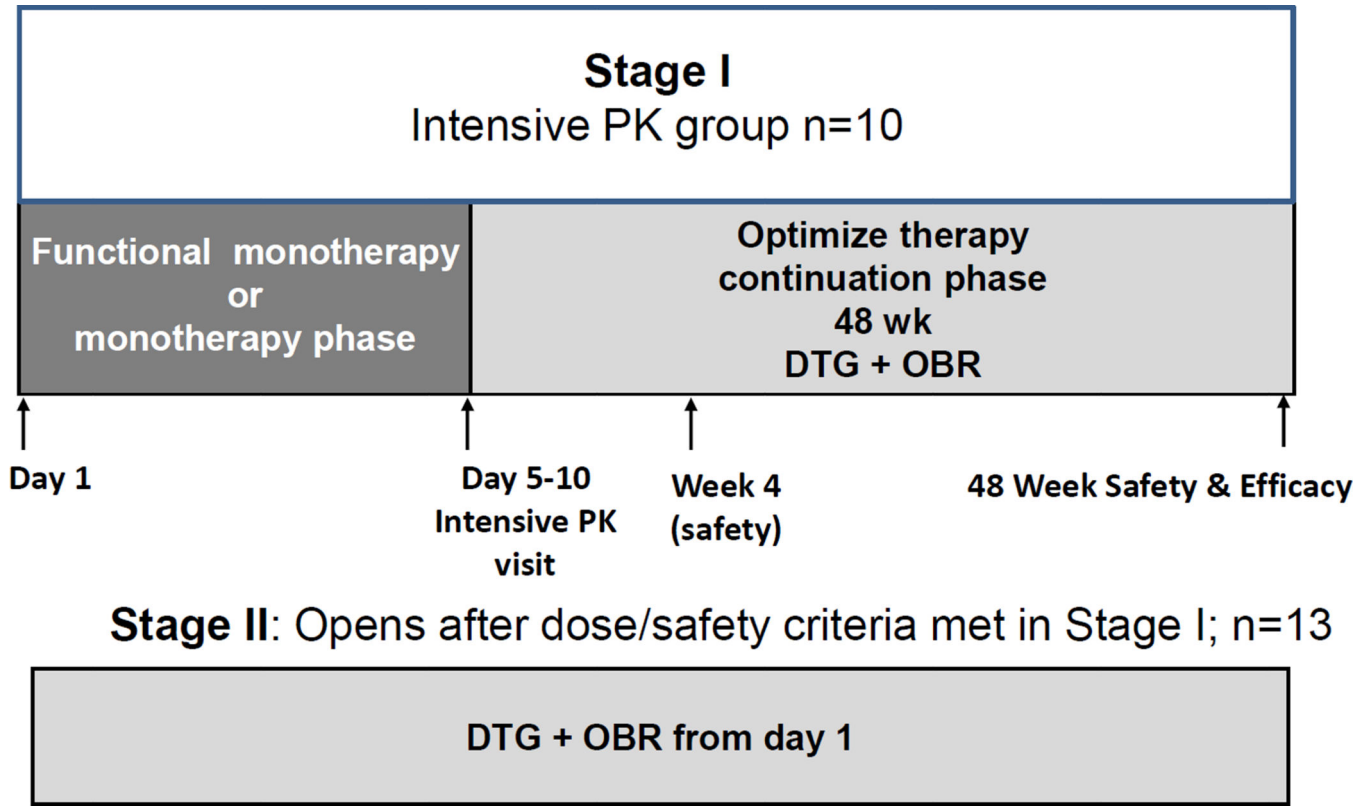
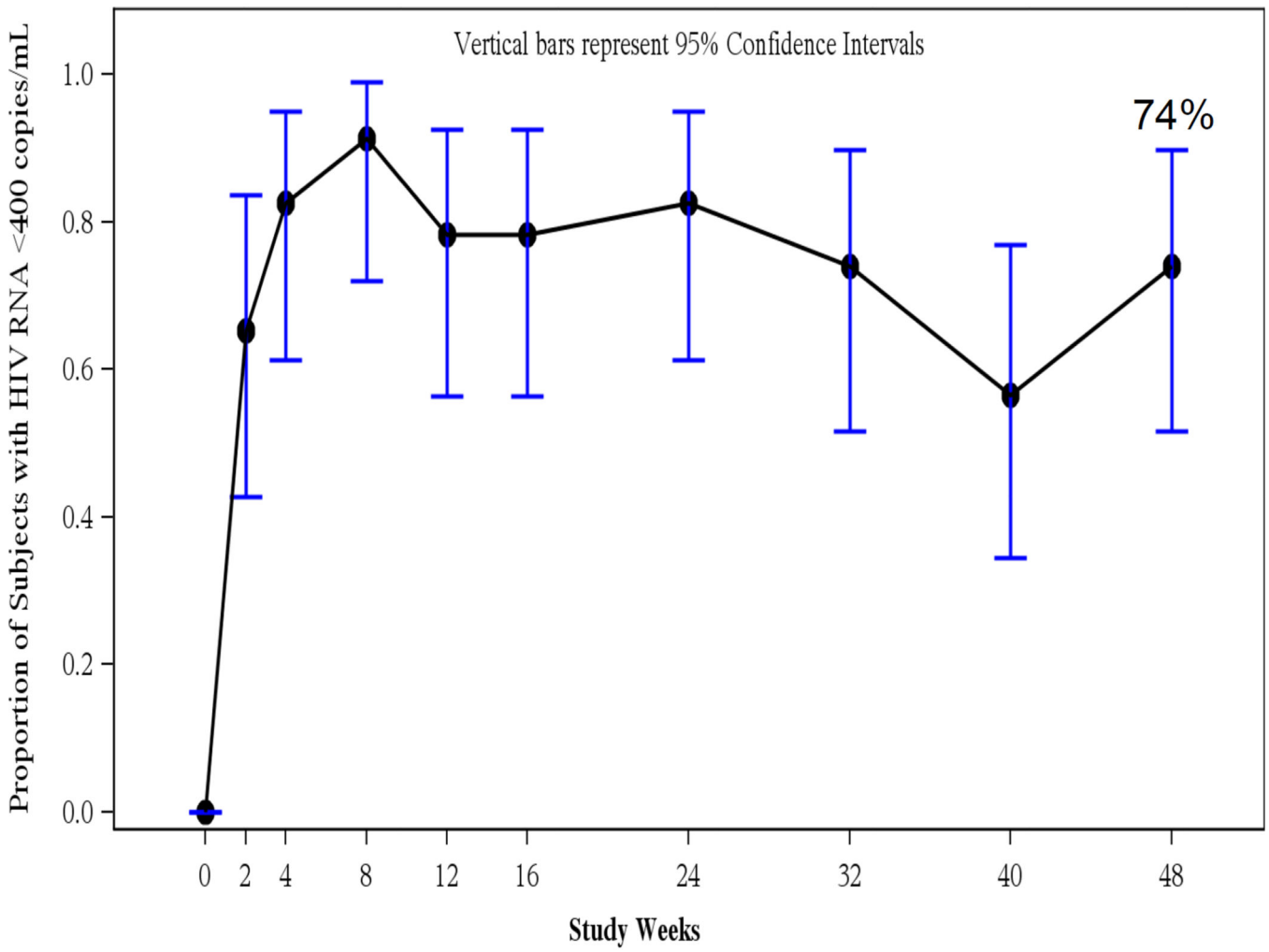


Figure 1.
Study design
OBR; optimized background regimen, DTG; dolutegravir

a



Number of subjects contributing data(n) out of total number of subjects in the cohort (N)

n	23	23	22	23	21	22	23	22	19	21
N	23	23	23	23	23	23	23	23	23	23

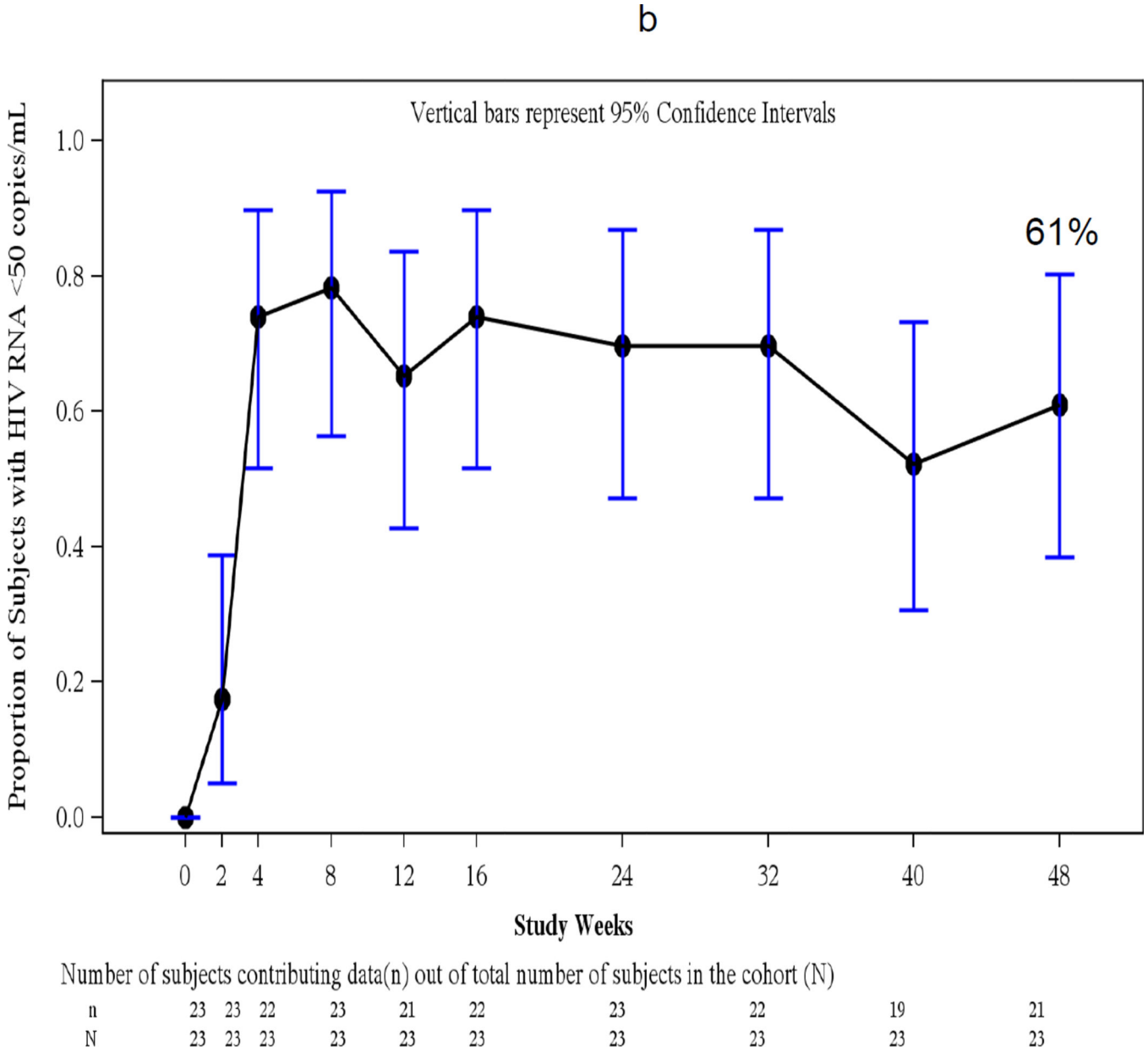


Figure 2.

a Proportion of participants with HIV RNA<400 copies/mL

b Proportion of participants with HIV RNA <50 copies/mL

Table 1

Patient demographic and baseline characteristics (N=23)

Age (years), median (IQR)	15 (12, 16)
Gender, n (%)	
Male	5 (22)
Female	18 (78)
Race, n (%)	
Black or African American	12 (52)
White	8 (35)
Asian	3 (13)
Ethnicity, Hispanic n, (%)	6 (26)
Plasma HIV-1 RNA Log_{10} copies/mL, median (IQR)	4.3 (3.9, 4.6)
CD4+ cell count (cells/μL), median (IQR)	466 (297, 771)
CD4+ percent (%), median (IQR)	22 (1, 39)
CDC HIV Classification, n (%)	
Stage 1	6 (26%)
Stage 2	5 (22%)
Stage 3	12 (52%)
Prior ART experience	
NRTI, n (%)	23 (100%)
PI, n (%)	18 (78%)
NNRTI, n (%)	12 (52%)
Triple class experienced, n (%)	8 (35%)
Previous ENF use, n (%)	2 (9%)
Time on prior ART (years), median (IQR)	12.5 (10.8, 14.0)
Weighted genotypic sensitivity score[a], n (%)	
2.0	5 (22%)
2.5	9 (39%)
3.0	2 (9%)
3.5	7 (30%)

ART: antiretroviral, NRTI: nucleoside reverse transcriptase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor, PI: protease inhibitor, ENF: enfuvirtide,

[a] weighted genotypic sensitivity score was calculated as previously described [31, 32]

Table 2

Dolutegravir pharmacokinetic parameters in Stage I (N=10)

	Mean (SD)	Median (min, max)	GM	CV%
Age (yr)	14.62 (±2.05)	14.11 (12.23, 17.86)	14.49	14.00
Weight (kg)	57.16 (±17.93)	50.85 (37.10, 91.40)	55.00	31.38
Dose (mg)	48.50 (±4.74)	50 (35, 50)	48.25	9.78
Dose (mg/kg)	0.90 (±0.19)	0.96 (0.55, 1.09)	0.88	21.50
$T_{1/2}$ (hr)	12.71 (±5.43)	10.44 (8.24, 24.80)	11.87	42.73
T_{max} (hr)		3.00 (1.00, 6.00)		
C_{max} (μg/mL)	3.82 (±1.46)	4.01 (1.15, 6.08)	3.48	38.36
C_{24} (μg/mL)	1.09 (±0.64)	1.14 (0.21, 2.12)	0.90	58.62
$AUC_{0–24}$ (μg.hr/mL)	51.57 (±22.24)	52.92 (13.05, 84.96)	43.13	45.97
CL/F (L/hr)	1.25 (±0.97)	0.87 (0.59, 3.83)	78.03	1.05

SD; standard deviation, min; minimum value, max; maximum value, GM; geometric mean, CV; coefficient of variation, $T_{1/2}$; half life, T_{max}; time to maximum plasma concentration, C_{max}; maximum plasma concentration, C_{24}; concentration 24 hours after dosing, $AUC_{0–24}$; area under the plasma concentration time curve from time of administration to 24 hours after dosing, CL/F; oral clearance.

Table 3

Drug resistance mutations for virologic failure (VL > 400 copies/mL) patients at week 48 (N=6)

#	HIV RNA (copies/mL) Baseline	HIV RNA (copies/mL) Virologic failure	OBR ART	Coding region	Baseline genotype	Virologic failure genotype
1	18,228	45,986	ABC, 3TC	RT	A98S, K103N	A98S, K103N
			ATV		M184V	M184V
				PR		
				IN		
2	10,902	2,307	TDF, FTC DRV/r	RT	D67N, V179I, M184V, K219Q	K219Q
				PR	L10I, K20R, L33V, M46L, I54L, A71V, V82A/F	L10I, L33V
				IN		
3	32,553	2,505	TDF, FTC	RT		
			ATV/r	PR	L10I	L10I
				IN		
4	7,739	13,722	TDF, FTC	RT		
				PR	I84V	M36I
				IN	L74L/M	R263R/K
5	23,499	3,002	TDF, 3TC	RT		
			LPV/r	PR		M36I, L89M
				IN		
6	7,155	16,506	DRV/r, ETR	RT	A62V, K65R	A62V, K65R
					K70R, V75I	K70R, V75I
					F77L, K101Q	F77L, K101Q
					K103N,F116Y	K103N,F116Y
					Q151M,P225H	Q151M,P225H
				PR	D30N, M46I	D30N, M46I
					Q58E A71T	Q58E, A71T
					N88D	N88D

#	HIV RNA (copies/mL) Baseline	HIV RNA (copies/mL) Virologic failure	OBR ART	Coding region	Baseline genotype	Virologic failure genotype
				IN		

#; participant, OBR; optimized background regimen, ART; antiretroviral therapy, ABC; abacavir, 3TC; lamivudine, ATV; atazanavir, TDF; tenofovir, FTC; emtricitabine, DRV/r; darunavir/ritonavir, ETR; etravirine, RT; reverse transcriptase, PR; protease, IN; integrase.