Bioequivalence of a Dolutegravir, Abacavir, and Lamivudine Fixed-Dose Combination Tablet and the Effect of Food

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Background: The integrase inhibitor dolutegravir and nucleoside analogues abacavir and lamivudine are once-daily treatment options for HIV. This study (NCT01622790) evaluated, first, the bioequivalence (BE) of a fixed-dose combination (FDC) tablet containing dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg (dolutegravir/abacavir/lamivudine FDC) vs coadministered dolutegravir 50 mg and abacavir/lamivudine combination tablets (Epzicom) and, second, the effect of food on the dolutegravir/abacavir/lamivudine FDC tablet.

Methods: Study part A (66 healthy subjects) was a single-dose, open-label, randomized, 2-period crossover study to evaluate the BE of the dolutegravir/abacavir/lamivudine FDC tablet and dolutegravir + abacavir/lamivudine tablets in the fasted state. In study part B, 12 subjects from part A received the dolutegravir/abacavir/lamivudine FDC tablet with a high-fat meal. BE and food effect were assessed by analysis of variance to determine the ratio of geometric least squares means and associated 90% confidence intervals for key pharmacokinetic parameters for each of dolutegravir, abacavir, and lamivudine.

Results: Sixty-two subjects completed part A. The dolutegravir/abacavir/lamivudine tablet was bioequivalent to the dolutegravir + abacavir/lamivudine tablets; 90% confidence intervals for the geometric least squares mean ratios fell within the 0.8–1.25 BE criteria. The effect of food on the dolutegravir/abacavir/lamivudine FDC tablet was similar to previous food effects observed with the separate formulations. The safety profile was comparable between treatments, with no observed serious or grade 3/4 adverse events.

Conclusions: The BE of the dolutegravir/abacavir/lamivudine FDC tablet was demonstrated; it may be administered without regard to meals.

Key Words: dolutegravir, integrase, pharmacokinetics, abacavir, lamivudine, fixed-dose combination

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INTRODUCTION

The advent of combination highly active antiretroviral therapy has dramatically improved clinical outcomes for patients with HIV. Currently available regimens are associated with a dramatic decrease in HIV-related morbidity and mortality through sustained suppression of viral load.[1,2] Early highly active antiretroviral therapy regimens were inconvenient for patients and required that 2 or 3 medications be dosed 2 or 3 times daily.[3] However, high levels of adherence are required to maintain virologic suppression and prevent the emergence of drug-resistant virus strains.[4] Therefore, considerable efforts have been devoted to the development of once-daily, single-tablet regimens (STRs) comprising multiple antiretroviral medications that can be administered once daily.[5]

Dolutegravir (Tivicay; ViiV Healthcare, Research Triangle Park, NC) is an unboosted inhibitor of the HIV integrase enzyme. It has recently been approved in the United States for the treatment of HIV in combination with other antiretroviral therapies.[6] Dolutegravir is predominantly metabolized by glucuronidation by UDP glucuronosyltransferase 1A1 (UGT1A1), with a minor contribution to metabolism by cytochrome P450 3A (CYP3A), resulting in a low propensity for drug interactions, a key feature that allows flexibility in coadministration with drugs that treat HIV comorbidities.[7,8] Dolutegravir exhibits a high barrier to resistance, lack of a requirement for pharmacokinetic (PK) boosting, and a plasma half-life that enables once-daily dosing in integrase inhibitor–naive subjects.[9–11] Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs) approved worldwide and available as a once-daily combination product (Epzicom, Kivexa; ViiV Healthcare).[12]

The combination of dolutegravir with these NRTIs represents a convenient, once-daily STR for use in HIV-infected patients without resistance to any of the components. This study was conducted to establish the bioequivalence (BE) of a dolutegravir/abacavir/lamivudine fixed-dose combination (FDC) tablet vs dolutegravir and abacavir/lamivudine (Epzicom) administered individually. Secondary objectives of the study were to assess the safety and tolerability of the FDC tablet and to determine the effects of food on the PK of the FDC tablet in a subset of subjects.

METHODS

Study Population

Healthy subjects between the ages of 18 and 55 years (inclusive) were eligible for enrollment in the study (NCT01622790) on the basis of medical history, physical examination, and laboratory tests. Subjects with a body weight ≥50 kg for men and ≥45 kg for women, with a body mass index within the range of 18.5–31.0 kg/m^2 (inclusive), were eligible. Prestudy screening levels of alanine aminotransferase, alkaline phosphatase, and bilirubin had to be ≤1.5 times the upper limit of normal for inclusion. A negative screening test for the *HLA-B*5701* allele was also required to minimize risk of abacavir hypersensitivity.[12,13]

Subjects with evidence of hepatitis B or hepatitis C infection or both within 3 months of screening, a positive test for HIV, or chronic liver disease were excluded. The use of prescription and nonprescription drugs, vitamins, and herbal and dietary supplements was prohibited within 14 days of the first dose of study medication and throughout the trial and follow-up visit. Subjects were also excluded if they participated in a recent clinical trial for other investigational drugs.

All enrolled subjects provided written informed consent. The study was approved by the Institutional Review Board for the study site (MidLands IRB, Overland Park, KS) and was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design

The study was a single-center, randomized, 2-part, open-label, crossover study in healthy adult subjects to evaluate the single-dose BE of an oral tablet containing dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg (dolutegravir/abacavir/lamivudine FDC) compared with the coadministration of the separate tablet formulations of dolutegravir 50 mg and the FDC of abacavir/lamivudine (600 mg/300 mg).

In part A of the study, subjects were randomized into 2 groups to receive treatment A (dolutegravir/abacavir/lamivudine FDC tablet) and treatment B (dolutegravir tablet plus a single abacavir/lamivudine tablet) in 1 of 2 sequences (A→B or B→A) following an overnight fast of at least 6 hours. During period 1 of part A, subjects received a single dose of the first treatment in the sequence followed by 48 hours of serial PK sample collection, with samples nominally collected predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours postdose. After a washout period of ≥7 days, period 2 of part A commenced, and subjects received the second treatment followed by 48 hours of serial PK sample collection at the same times noted for period 1. Subjects who participated only in part A had a follow-up visit 7–14 days after the last dose of study drug.

For study part B, the first 12 subjects who completed the first 2 dosing periods (part A), and who were interested in returning for a third period, were assigned to receive a single dose of the dolutegravir/abacavir/lamivudine FDC tablet with a high-fat meal (treatment C; estimated 869 calories with 53% fat) that was identical in composition to the example meal recommended by the Food and Drug Administration.[14] There was a ≥7-day washout period between parts A and B. PK sampling over 48 hours for part B was as noted above for part A. Subjects returned for a follow-up visit 7–14 days after the dose of study drug in part B. With respect to both BE (part A) and food effect (part B) evaluations, the study was designed and conducted according to Food and Drug Administration guidance documents.[14,15] Safety assessments were performed throughout the study and included adverse event (AE) monitoring, clinical laboratory tests, vital signs, and electrocardiograms.

Bioanalytical Methods

Plasma samples were analyzed for dolutegravir, abacavir, and lamivudine concentrations by Pharmaceutical Product Development (PPD; Middleton, WI). Analysis was performed using validated analytical methods based on protein precipitation, followed by high-performance liquid chromatography with tandem mass spectrometry analysis. The lower and higher limits of quantification for dolutegravir were 20 and 20,000 ng/mL, respectively, using a 25-μL aliquot of EDTA-treated plasma. For abacavir and lamivudine, the lower and higher limits of quantification were 2.5 and 2500 ng/mL, respectively, using a 50-μL aliquot of EDTA-treated plasma. Linear regression analysis calculations were performed using PPD Assist LIMS, version 5.

Quality control samples, prepared at 5 different concentrations for each analyte and stored under the same conditions as study samples, were analyzed with each batch of samples against separately prepared calibration standards. The bias for the analysis of dolutegravir was −2.3%–1.7%, with precision values of 3.4%–4.7% (within-day) and ≤2.3% (between-day). The bias for the analysis of abacavir was −3.0%–3.2%, with precision values of 3.7%–7.6% (within-day) and ≤1.4% (between-day). The bias for the analysis of lamivudine was −1.4%–1.9%, with precision values of 3.4%–7.4% (within-day) and ≤2.4% (between-day).

Pharmacokinetic Analysis

Pharmacokinetic analyses of plasma dolutegravir, abacavir, and lamivudine concentration–time data were conducted using noncompartmental Model 200 of WinNonlin Professional Edition version 5.3 (Pharsight Corporation, Mountain View, CA). Actual sampling times relative to time of dose administration were used for the analysis. The primary PK parameters of interest were the exposure parameters of peak concentration observed maximum plasma concentration (Cmax), area under the concentration–time curve to the last postdose quantifiable concentration (AUC_{0-t}) and the AUC extrapolated to infinity($AUC_{0-\infty}$).

Concentration–time data for a given subject and treatment were excluded from PK parameter estimation if emesis occurred within 6 hours after dose administration or if

there were any missing PK samples within the same post-dose interval.

Statistical Analysis

A total sample size of 60 subjects was estimated to provide 90% power to demonstrate BE of the dolutegravir/abacavir/lamivudine FDC tablet compared with coadministration of dolutegravir and abacavir/lamivudine, with the following assumptions: each of the 2 one-sided comparisons was made at the 5% level for all analytes; a true ratio of 0.9; and the highest within-subject variability of 22%. A 10% enrollment overage was added to account for potential subject dropouts, resulting in a total sample size of 66 subjects.

Demographic data and PK parameters were summarized using descriptive statistics. Following $\log_e$-transformation, the PK parameters for each analyte were analyzed using a mixed effects model. Analysis of variance was performed using SAS mixed linear models procedure (SAS, Cary, NC) to assess BE and the effect of food on the PK parameters. The model for the BE assessment included sequence, period, and treatment as fixed effects and subject within sequence as a random effect. For food effect analysis, the model included a fixed effect term for treatment and a random effect term for subject. Point estimates and their associated 90% confidence intervals (CIs) were constructed for the differences in the log-transformed parameters, test treatment − reference treatment (A − B for BE assessment; C − A for food effect evaluation). The point estimates and their associated 90% CIs were then back-transformed to provide point estimates for the ratio of geometric least squares means and associated 90% CIs on the original scale.

RESULTS

Subject Demographics and Disposition

Subject demographics and disposition are summarized in Table 1. Sixty-six subjects were enrolled in the study, and 62 completed part A as planned. During part A of the study, 3 subjects were withdrawn and 1 was lost to follow-up. One of the withdrawals was because of emesis after dosing with the FDC, and the second was because of an inability to swallow the abacavir/lamivudine tablet. A third subject did not have a 2-hour PK sample collected and, therefore, was not evaluable for the PK analysis. No subjects withdrew during part B of the study; 12 subjects completed it as planned. Overall, the mean age was 29.3 years, and most subjects were men (66%). The predominant racial groups were Caucasian (52%) and African American (38%).

Pharmacokinetics

The PK analysis comprised 62 subjects for part A of the study and 12 subjects for part B. Plasma PK parameter estimates for dolutegravir, abacavir, and lamivudine from the 2-period BE portion of the study (part A) and from the food–effect component of the study (part B) are summarized in Table 2.

Results from the statistical analyses for BE between the FDC tablet and the dolutegravir + abacavir/lamivudine coadministered tablets, as well as from the effect of food on the FDC tablet, are summarized in Table 2. With regard to the BE assessment, the 90% CIs for the geometric least squares mean ratios of Cmax and AUC were all within the 0.80–1.25 BE criteria for each of dolutegravir, abacavir, and lamivudine (Fig. 1).

TABLE 1. Subject Disposition and Demographics

Parameter	FDC Fasted	Dolutegravir + Abacavir/Lamivudine Fasted	Overall	FDC Fed
Subject disposition, n (%)				
Planned subjects	66	66	66	12
Randomized subjects	65	65	66	12
Subjects completed as planned	63 (97)	62 (95)	62 (94)	12
Subject demographics				
Age, mean (SD), yrs	29.3 (9.59)	29.3 (9.55)	—	33.8 (11.06)
Sex, n (%)				
Male	43 (66)	43 (66)	—	8 (67)
Female	22 (34)	22 (34)	—	4 (33)
BMI, mean (SD), kg/m^2	25.03 (3.72)	25.16 (3.71)	—	26.48 (3.09)
Height, mean (SD), cm	172.55 (10.01)	172.58 (9.97)	—	175.86 (11.64)
Weight, mean (SD), kg	74.69 (13.72)	75.05 (13.48)	—	82.29 (14.75)
Ethnicity, n (%)				
Hispanic or Latino	7 (11)	7 (11)	—	1 (8)
Non-Hispanic or Latino	58 (89)	58 (89)	—	11 (92)
Race, n (%)				
African American/African heritage	25 (38)	25 (38)	—	5 (42)
American Indian or Alaskan native	3 (5)	3 (5)	—	0
Asian—East Asian Heritage	3 (5)	3 (5)	—	0
White, Caucasian/European heritage	34 (52)	34 (52)	—	7 (58)

BMI, body mass index.

TABLE 2. Statistical Comparison of Plasma Dolutegravir, Abacavir, and Lamivudine PK Parameters for BE and Food Effect Assessment*

	BE Assessment			Food Effect Assessment		
PK Parameter	FDC Fasted GLS Mean (n = 62)	Dolutegravir + Abacavir/ Lamivudine Fasted GLS Mean (n = 62)	Ratio of GLS Mean (90% CI)	FDC Fasted GLS Mean (n = 12)	FDC Fed GLS Mean (n = 12)	Ratio of GLS Mean (90% CI)
Dolutegravir						
$AUC_{0-\infty}$, $\mu g \cdot h \cdot mL^{-1}$	44.73	47.36	0.945 (0.889 to 1.0)	40.54	60.11	1.48 (1.36 to 1.62)
AUC_{0-t}, $\mu g \cdot h \cdot mL^{-1}$	40.86	43.34	0.943 (0.888 to 1.0)	37.38	54.85	1.47 (1.35 to 1.60)
Cmax, μg/mL	2.44	2.54	0.961 (0.906 to 1.02)	2.25	3.08	1.37 (1.26 to 1.48)
Abacavir						
$AUC_{0-\infty}$, $\mu g \cdot h \cdot mL^{-1}$	13.92	14.51	0.960 (0.939 to 0.980)	12.96	12.0	0.926 (0.899 to 0.953)
AUC_{0-t}, $\mu g \cdot h \cdot mL^{-1}$	13.90	14.48	0.960 (0.939 to 0.980)	12.94	11.96	0.924 (0.898 to 0.952)
Cmax, μg/mL	4.03	4.38	0.920 (0.867 to 0.977)	3.84	2.97	0.774 (0.662 to 0.905)
Lamivudine						
$AUC_{0-\infty}$, $\mu g \cdot h \cdot mL^{-1}$	12.75	13.12	0.972 (0.940 to 1.01)	12.08	12.61	1.04 (0.971 to 1.12)
AUC_{0-t}, $\mu g \cdot h \cdot mL^{-1}$	12.30	12.81	0.960 (0.928 to 0.994)	11.61	12.18	1.05 (0.963 to 1.14)
Cmax, μg/mL	2.11	2.28	0.926 (0.885 to 0.968)	1.95	1.87	0.960 (0.879 to 1.05)

*Values are given as geometric mean.
AUC_{0-t}, area under the concentration–time curve from time 0 to the time of the last quantifiable concentration; $AUC_{0-\infty}$, AUC extrapolated to infinity; GLS, geometric least squares.

Following administration of the dolutegravir/abacavir/lamivudine FDC with a high-fat meal, the plasma exposures of dolutegravir were approximately 48% higher for AUC and 37% higher for Cmax compared with administration in the fasted state (Table 2). The Cmax for abacavir was approximately 23% lower when administered with food; however, all other primary PK values for abacavir and lamivudine were similar with or without food.

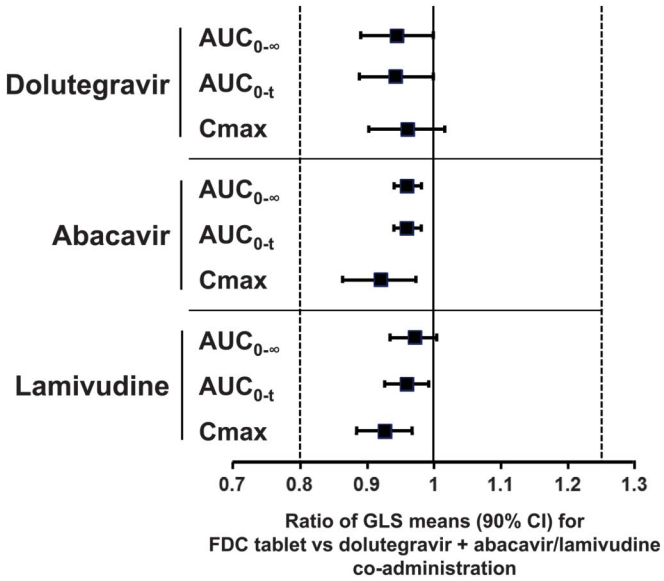

FIGURE 1. Assessment of BE. Ratios of GLS means and 90% CIs (dolutegravir/abacavir/lamivudine FDC tablet vs separate dolutegravir + abacavir/lamivudine tablet coadministration) for primary PK parameters. A ratio of 1 is marked with a vertical solid line, and the criteria for BE (90% CI of ratio within 0.8–1.25) are denoted with vertical dotted lines. AUC_{0-t}, area under the concentration–time curve from time 0 to time of the last quantifiable concentration; $AUC_{0-\infty}$, AUC extrapolated to infinity; GLS, geometric least squares.

Safety

All 66 subjects enrolled in the study received at least 1 dose of study medication and thus were included in the safety evaluation. The most common AEs reported were nausea and headache. Incidences of all drug-related AEs observed in the study are summarized in Table 3. Tolerability was similar between the 2 treatments; however, the incidence of nausea was higher in the group receiving dolutegravir and abacavir/lamivudine separately (28%) compared with the group receiving the dolutegravir/abacavir/lamivudine FDC (15%). One AE led to withdrawal from the study; the subject experienced emesis 41 minutes after FDC tablet administration in period 2. No serious AEs and no grade 3 or 4 AEs were observed. There were no reported AEs from administration of the dolutegravir/abacavir/lamivudine FDC tablet with food to the 12 subjects in part B.

DISCUSSION

This study demonstrates that the dolutegravir/abacavir/lamivudine FDC tablet containing dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg is bioequivalent to coadministered commercially available separate tablets for dolutegravir and abacavir/lamivudine. Cmax and AUC PK parameters for all 3 drugs were within established criteria. The effect of food was evaluated in a subset of subjects to confirm previous findings with the separate entities. Administration of the dolutegravir/abacavir/lamivudine FDC tablet with a high-fat meal did not result in clinically significant differences in plasma exposure for any of the 3 components.

TABLE 3. Summary of Drug-Related AEs in Part A*

Drug-Related AEs†	FDC (n = 65)	Dolutegravir + Abacavir/Lamivudine (n = 65)
Any drug-related AE	12 (18)	18 (28)
Nausea	10 (15)	18 (28)
Headache	2 (3)	4 (6)
Abdominal pain	0	1 (2)
Emesis	1 (2)	0
Dizziness	1 (2)	0
Feeling hot	0	1 (2)

Values are given as n (%).
*No AEs were reported in part B.
†Occurring in 2 or more subjects in any treatment group.

The 48% and 37% increases in dolutegravir AUC and Cmax values, respectively, following administration with a high-fat meal are similar to previous observations when dolutegravir was administered alone with food.[16] Additionally, although there was an observed 23% decrease in abacavir Cmax following administration with a high-fat meal, this was also consistent with previous studies.[17–19] Thus, the dolutegravir/abacavir/lamivudine tablet can be administered with or without food as indicated in the labeling for the separate entities.[6,12]

The PK exposures in this study following administration of the FDC tablet are consistent with exposure data for separate components as obtained in previous studies. While there are limitations to cross-study comparisons, the PK values for abacavir and lamivudine were comparable between administration of dolutegravir/abacavir/lamivudine FDC in this study and when abacavir and lamivudine were given without dolutegravir (Table 4).[18] These data indicate that no clinically significant drug interactions occur, as expected, because these drugs are metabolized and eliminated by different pathways.[8,10,12,20,21]

The BE and food effect PK data from this study support the development of an FDC tablet containing dolutegravir, abacavir, and lamivudine, which can be administered without regard to meals. The combination of these 3 drugs into a once-daily tablet results in a new STR for the treatment of HIV with a favorable safety and efficacy profile. Dolutegravir in combination with abacavir/lamivudine has been shown to be superior to the FDC of efavirenz/tenofovir/emtricitabine in treatment-naive subjects with regard to percentage of subjects with HIV-1 RNA <50 copies per mL (88% vs 81%; $P = 0.03$).[22] The combination of dolutegravir and abacavir/lamivudine was also shown to be effective in the SPRING-2 study, which demonstrated noninferiority between dolutegravir and raltegravir in combination with 2 NRTIs selected by the investigator. In the dolutegravir-containing arm, virologic response was similar between dolutegravir with abacavir/lamivudine and dolutegravir with tenofovir/emtricitabine.[23] Further support for the dolutegravir/abacavir/lamivudine regimen was provided in the FLAMINGO study, where dolutegravir was shown to be superior to darunavir/ritonavir in the percentage of subjects with HIV-1 RNA <50 copies per mL at 48 weeks with backbone NRTIs selected by the investigator (90% vs 83%; $P = 0.025$).[24] In this study, the choice of NRTIs did not affect the virologic response. These large clinical trials all demonstrate that the combination of dolutegravir, abacavir, and lamivudine is a safe and effective regimen for HIV-infected patients.

An STR option comprising dolutegravir, abacavir, and lamivudine may offer multiple advantages for patients and clinicians. This multitarget STR is of similar size to other tablets containing 3 or 4 antiretroviral medications (22 × 11 mm, approximately 1.7 g). It inhibits 2 of the 3 virally encoded enzymes (reverse transcriptase and integrase) in the viral replication cycle, has been shown to be safe and effective in large phase III studies, and exhibits a high barrier to the development of viral resistance. Metabolism of the components in the dolutegravir/abacavir/lamivudine FDC tablet is carried out primarily by glucuronidation (for dolutegravir and abacavir) or renal excretion (for lamivudine), thus minimizing drug–drug interactions through the CYP450 pathway.[7,8,19,21] No PK "booster" is required, further reducing a need for dose adjustments or substitutions of concomitant medications. In achieving BE of the dolutegravir/abacavir/lamivudine FDC tablet, a greater potential for increased compliance, convenience, and treatment outcomes is provided when compared

TABLE 4. Comparison of Abacavir and Lamivudine PK Parameters Across Studies*

	BE Study for Abacavir/Lamivudine FDC vs Abacavir + Lamivudine†		This Study	
PK Parameter	Abacavir/Lamivudine FDC (n = 25)	Abacavir + Lamivudine (n = 25)	Dolutegravir/Abacavir/ Lamivudine FDC (n = 62)	Dolutegravir + Abacavir/ Lamivudine (n = 62)
Abacavir				
$AUC_{0-\infty}$, $\mu g \cdot h \cdot mL^{-1}$	14.21 (23)	14.18 (23)	13.91 (26)	14.50 (24)
AUC_{0-t}, $\mu g \cdot h \cdot mL^{-1}$	14.18 (23)	14.15 (23)	13.89 (26)	14.48 (24)
Cmax, μg/mL	4.69 (31)	4.91 (24)	4.02 (24)	4.37 (26)
Lamivudine				
$AUC_{0-\infty}$, $\mu g \cdot h \cdot mL^{-1}$	12.57 (19)	13.18 (19)	12.76 (25)	13.12 (21)
AUC_{0-t}, $\mu g \cdot h \cdot mL^{-1}$	12.34 (19)	12.95 (19)	12.31 (26)	12.81 (21)
Cmax, μg/mL	2.64 (27)	2.82 (19)	2.11 (29)	2.28 (26)

*Values are given as geometric mean (coefficient of variation %).
†CAL10001 study (data on file; ViiV Healthcare).[16]
ABC, abacavir; AUC_{0-t}, area under the concentration-time curve from time 0 to time of last quantifiable concentration; $AUC_{0-\infty}$, AUC extrapolated to infinity; DTG, dolutegravir; 3 TC, lamivudine.

with regimens requiring multiple pills per day.[25] The data presented in this study demonstrate the BE of an FDC tablet containing dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg to separately administered tablets. The dolutegravir/abacavir/lamivudine STR will provide an important new option for people living with HIV.

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