Clinical Infectious Diseases

BRIEF REPORT

Dolutegravir Plus Lamivudine Maintains Human Immunodeficiency Virus-1 Suppression Through Week 48 in a Pilot Randomized Trial

Babafemi O. Taiwo,[1] Vincent C. Marconi,[2] Baiba Berzins,[1] Carlee B. Moser,[3] Amesika N. Nyaku,[4] Carl J. Fichtenbaum,[5] Constance A. Benson,[6] Timothy Wilkin,[7] Susan L. Koletar,[8] Jonathan Colasanti,[2] Edward P. Acosta,[9] Jonathan Z. Li,[10] and Paul E. Sax[11]

[1]Division of Infectious Diseases, Northwestern University, Chicago, Illinois, [2]Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia, [3]Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, [4]Division of Infectious Diseases, Rutgers University, Newark, New Jersey, [5]Department of Internal Medicine, University of Cincinnati, Ohio, [6]Division of Infectious Diseases and Global Public Health, University of California, San Diego, [7]Division of Infectious Diseases, Weill Cornell Medicine, New York, New York, [8]Division of Infectious Diseases, The Ohio State University, Columbus, [9]Department of Pharmacology and Toxicology, University of Alabama at Birmingham, and [10]Division of Infectious Diseases, Brigham and Women's Hospital and [11]Harvard Medical School, Boston, Massachusetts

(See Major Article by Taiwo et al on pages 1689–1697.)

In this randomized pilot clinical trial, dolutegravir plus lamivudine was noninferior to continuation of standard 3-drug maintenance antiretroviral therapy. There was no emergence of drug resistance in the participant who experienced virologic failure while receiving dolutegravir plus lamivudine.

Clinical Trials Registration: NCT02263326.

Keywords. Dolutegravir; lamivudine; 2-drug; maintenance therapy.

Some 2-agent antiretroviral regimens have demonstrated comparable efficacy to 3-agent regimens for maintenance therapy [1–5]. Adoption of 2-agent maintenance therapy in routine practice would be enhanced by a regimen that combines efficacy, convenience, limited drug-drug interactions, long-term tolerability and safety. We investigated dolutegravir (DTG) plus lamivudine (3TC) in the pilot Antiretroviral Strategy to Promote Improvement and Reduce Exposure (ASPIRE) study (ClinicalTrails.gov NCT02263326).

METHODS

Study Population

ASPIRE was an open-label, randomized, multicenter, 48-week clinical trial in adults infected with human immunodeficiency virus type 1 (HIV-1), virologically suppressed with any US Department of Health and Human Services–recommended alternative or other 3-agent regimen for ≥48 weeks. Inclusion criteria were age ≥18 years, ≥2 HIV-1 RNA (viral load [VL]) measurements <50 copies/mL within 48 weeks of screening, a screening VL <20 copies/mL, creatinine clearance ≥50 mL/min, no history of virologic failure (VF) after 1 year of therapy, a pretreatment genotype documenting no nucleos(t)ide reverse-transcriptase (RT) resistance mutations, and no known integrase resistance mutations [6].

Pregnant or breastfeeding women and individuals with chronic hepatitis B infection, severe liver disease, or planned hepatitis C treatment during the study period were excluded. A prior switch for simplification or tolerability was allowed. The institutional review board of each participating institution approved this study, and each participant provided informed consent.

Study Procedures

Eligible participants were randomized 1:1 to switch to open label oral DTG (50 mg) plus 3TC (300 mg once daily) (DTG + 3TC) given as separate pills or to continue 3-agent antiretroviral therapy (cART). Postentry monitoring included VL, CD4/CD8 T-cell count, safety monitoring, lipid profile, and 4-day adherence recall. VL measurements were performed using the COBAS AmpliPrep/COBAS TaqMan HIV-1 test (version 2.0), with a detection limit of 20 copies/mL (Roche Molecular Systems). VF was defined as confirmed VL >50 copies/mL within 35 days of the initial result. At VF, protease/RT and integrase genotyping were performed on the VF confirmation plasma sample, and DTG concentrations were assayed with a dynamic range of 5.0–10 000 ng/mL [7].

Statistical Methods

The primary analysis compared the proportion of participants in each arm with treatment failure (defined as VF, loss to follow-up, or treatment discontinuation/modification) by week 24 to determine whether DTG/3TC was noninferior to cART. We considered DTG/3TC noninferior if the 90% confidence interval (CI) for the difference in proportions, calculated with Miettinen-Nurminen (score) confidence limits, excluded the 12% noninferiority margin. A secondary analysis of treatment failure included only participants with VF. Virologic outcomes, based on the Food and Drug Administration (FDA) snapshot algorithm at weeks 24 and 48, were also compared, with corresponding 95% CIs.

Viral blips (ie, VL >50 copies/mL preceded and followed by ≤50 copies/mL), emergent antiretroviral resistance, and adverse events of grade ≥3 or that led to treatment modification or discontinuation regardless of grade were tabulated; no statistical tests were done. Wilcoxon rank sum tests were used to contrast baseline characteristics and assess changes in CD4 cell count, lipids and creatinine clearance. All baseline comparisons and secondary inferences was assessed with a 5% type I error rate.

Received 23 November 2017; editorial decision 18 December 2017; accepted 22 December 2017; published online December 21, 2017.

Correspondence: B. O. Taiwo, Division of Infectious Diseases, Northwestern University, Feinberg School of Medicine, 645 N Michigan Ave, Ste 900, Chicago, IL 60611 (b-taiwo@northwestern.edu).

Clinical Infectious Diseases® 2018;66(11):1794–7

DOI: 10.1093/cid/cix1131

A sample size of 41 participants per arm provided 80% power to show noninferiority of DTG/3TC to cART based on a 12% noninferiority margin, assuming an estimated treatment failure rate of 5% per arm by week 24 and 5% 1-sided type I error rate. The sample size was inflated by 10% to account for potential loss to follow-up, resulting in the target sample size of 45 participants per arm.

RESULTS

Of 105 participants screened, 15 were excluded by laboratory result (n = 9), antiretroviral therapy (ART) history (n = 2), unavailable pretreatment genotype (n = 1), or participant withdrawal (n = 3). Ninety participants were randomized (45 per arm); 1 participant did not initiate study treatment and was excluded, resulting in 89 participants (44 DTG/3TC and 45 cART) included in the analysis. This treatment exposed population was 88% male and 60% white, 38% black, and 15% Hispanic, with a median age of 47 years (interquartile range [IQR], 38–54 years), a median ART exposure of 5.7 years (3.7–7.5 years), and median entry CD4 cell count of 680/μL (498–927/μL). Prerandomization regimens included integrase inhibitors (37%), protease inhibitors (33%), or nonnucleoside RT inhibitors (30%). Eighty-six percent of participants were receiving tenofovir disoproxil fumarate/emtricitabine and abacavir/3TC. Baseline parameters were comparable between arms.

In the primary analysis at week 24, treatment failure occurred in 3 of 44 (6.8%) receiving DTG/3TC and 3 of 45 (6.7%) receiving cART (0.15% difference; 90% CI, −9.8 to 10.2), demonstrating noninferiority of DTG/3TC. The 3 participants with treatment failure at week 24 in the DTG/3TC arm comprised 1 with VF, 1 lost to follow-up, and 1 with treatment discontinuation due to an adverse event (constipation), whereas the 3 with treatment failure in the cART arm included 1 lost to follow up and 2 with regimen simplifications. Using the FDA snapshot algorithm, VL was <50 copies/mL at week 24 in 41 of 44 participants in the DTG/3TC arm (93.2%) versus 41 of 45 (91.1%) in the cART arm (difference, 2.1%; 95% CI, 11.2%–15.3%; $P = .71$); and at week 48 in 90.9% versus 88.9% (difference 2.0%; 95% CI, −12.6% to 16.5%; $P = .76$). Ninety-two percent of participants reported perfect adherence.

The only participant with VF (DTG/3TC arm at week 24) had no emergent RT or integrase resistance mutations, and this participant remained viremic after switching to darunavir-cobicistat plus abacavir-3TC (Table 1). This participant reported good adherence and had therapeutic DTG concentrations. Viral blips were uncommon in both arms, occurring once in a participant randomized to DTG/3TC and at 1 time point each in 4 participants receiving cART (Table 2).

From baseline through week 48, the median changes (IQR) between the DTG/3TC and cART arms, respectively, were similar for CD4 cell count (39/μL [IQR, −71/μL to 188/μL] vs 28 (−36 to 83) ; total cholesterol (0 [−31 to 31) vs −1 [−13 to 9] mg/dL); low-density lipoprotein (+2 [−19 to 27] vs −3 [−16 to 10] mg/dL), and triglycerides (−9 [−58 to 37] vs + 4 [−17 to 41] mg/dL (all $P > .2$) and creatinine clearance (−4 [−14 to 4) vs 0 [−6 to 5] mL/min; $P = .07$).

Grade 3 laboratory adverse events affected glucose (n = 2), low-density lipoprotein (n = 1), and alanine transaminase (n = 1) in the DTG/3TC arm, and bilirubinemia (n = 3) in the cART arm. Clinical adverse events included grade 3 diabetes (n = 2), back pain (n = 1), osteoarthritis (n = 1), fall with loss of consciousness (n = 1), and grade 4 viral syndrome (n = 1) in the DTG/3TC arm and grade 3 diarrhea (n = 1), nephrolithiasis (n = 1), and grade 4 myocardial infarction (n = 2) in the cART arm. One participant discontinued DTG/3TC owing to grade 2 constipation.

DISCUSSION

In this randomized pilot clinical trial, switching to the 2-agent regimen of DTG/3TC was noninferior at 24 weeks to

Table 1. Findings in Participant With Virologic Failure

	Week of Treatment							
Finding	0	4	12	24	31 (Switch to DRV/c + ABC/3TC)	34	36	48
VL (copies/mL)	<20	21	48	375/235[a]	…	528	264	85
Genotype: RT, PI, integrase	…	…	…	No mutations	…	…	…	…
DTG concentration, ng/mL[b]	…	3210	1553	3115/2828[a]	…	<5	…	…
Missed doses in last 4 d (participant report)		None	None	None	…	None	None	None
Study treatment	DTG/3TC	DTG/3TC	DTG/3TC	DTG/3TC	…	DRV/c + ABC/3TC	DRV/c + ABC/3TC	DRV/c + ABC/3TC

Abbreviations: 3TC, lamivudine; ABC, abacavir; DRV/c, darunavir/cobisistat; DTG, dolutegravir; PI, protease inhibitor; RT, reverse transcriptase; VL, viral load.

[a]Initial/confirmatory value.

[b]DTG concentration required to inihibit 90% viral replication in vitro (IC_{90}) is 64 ng/mL [8].

Table 2. Viral Blips

Treatment Arm of Participant	VL, Copies/mL					
	Week 0	Week 4	Week 12	Week 24	Week 36	Week 48
DTG/3TC	<20	<20	191/<20[a]	<20	<20	<20
Continuing ART	<20	<20	351/<20[a]	<20	<20	<20
Continuing ART	<20	<20	<20	<20	<20	179/30[a]
Continuing ART	<20	682/<20[a]	<20	<20	<20	<20
Continuing ART	2268	50	31	<20	<20	<20

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; DTG, dolutegravir; VL, viral load.

[a]Initial/confirmatory VL.

continuation of standard 3-drug maintenance therapy. This was supported by the FDA snapshot analyses at weeks 24 and 48.

The efficacy of maintenance DTG/3TC in this study is consistent with the results of the single-arm LAMIDOL trial [9]. DTG is an integrase inhibitor with high antiviral potency and high resistance barrier. Since its approval in 1995, 3TC has been a key component of antiretroviral regimens with excellent tolerability and safety. By avoiding both a third active antiretroviral agent and a pharmacologic booster, DTG/3TC has few drug-drug interactions and a potential for long-term safety and tolerability. This regimen also has no major dietary restrictions, with the potential for coformulation into a single tablet that, with generic 3TC, can lower the cost of ART [10]. If its efficacy is confirmed, DTG/3TC could become a novel option for maintenance ART.

In this study, 1 participant in the DTG/3TC arm experienced VF. It is intriguing that this participant had adequate DTG concentrations and no evidence of RT or integrase resistance on population sequencing. Although sporadic adherence cannot be excluded, it is reassuring that the participant's future treatment options were not compromised. Emergence of RT and integrase mutations was described recently in a suboptimally adherent treatment-naive patient in whom DTG/3TC failed [11]. Viral blips were uncommon overall and occurred only once in the DTG/3TC arm, an encouraging finding because frequent viral blips have been associated with suboptimal virologic outcomes [12]. An analysis of participants in this study using an experimental single copy assay is ongoing.

The regimen of DTG/3TC has several advantages over other virologically effective 2-drug combinations. Specifically, boosted protease inhibitor plus 3TC regimens [3–5] have a greater risk of drug interactions and metabolic complications, whereas DTG plus rilpivirine [1] is limited by food requirement and the need to avoid acid-reducing therapies. Long-acting cabotegravir plus rilpivirine [2] must be administered intramuscularly and hence may be unappealing to some patients. Of note, DTG/3TC and these other 2-agent regimens are contraindicated in individuals with chronic hepatitis B infection.

Strengths of our study include its randomized design and high retention rate. Its major limitation is its small sample size; the FDA stipulation of a margin of 4% for comparative noninferiority studies of switch strategies occurred after ASPIRE was designed. The generalizability of the results is further limited by the open-label design, high study entry CD4 cell count, the long duration of prior HIV treatment, and the exclusion of individuals with a history of VF or unavailable baseline genotype. Despite these limitations, we found that DTG/3TC maintained viral suppression as well as 3-agent ART in this pilot randomized trial. These results justify the planned fully powered clinical trial of the regimen (TANGO; Clinical Trials.gov NCT02831673).

Notes

Acknowledgments. We acknowledge Patrick Janulis, Rachelle Price, Sherrie Wolfe, and Jane Regalado (Northwestern University); Cheryl Keenan (Brigham and Women's Hospital); Kishna Outlaw, Hsin Chien, and the Emory Center for AIDS Research (P30AI050409) (Emory University); Heather Harber (The Ohio State University); Fran Hyc and Eva Whitehead (University of Cincinnati); Helen King, and Edward Seefried (University of California at San Diego); and Todd Stroberg and Valery Hughes (Weill Cornell Medicine). This publication was made possible with help from the Third Coast Center for AIDS Research (CFAR), an NIH funded center (P30 AI117943). Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Northwestern University (NU), which is supported by the NU Clinical and Translational Science Institute, an NIH funded National Center for Advancing Translational Sciences (UL1TR001422).

Disclaimer. This publication does not represent the official views of ViiV Healthcare.

Financial support. This work was supported by an investigator-sponsored study grant from ViiV HealthCare to Northwestern University (NU). ViiV Healthcare and GlaxoSmithKline provided funding and the study drugs.

Potential conflicts of interest. B. O. T. has served as a paid consultant to ViiV, Gilead, and Janssen and on the Clinical Care Options speakers bureau and has received grant funding to his institution from ViiV/GlaxoSmithKline (GSK). V. C. M., C. J. F., C. A. B., T. W., S. L. K., J. C., and P. E. S. have received grant funding for this study to their institutions through NU from ViiV/GSK. C. B. M. has received a consulting fee from NU. C. J. F. has received payment for service on the Clinical Care Options speakers bureau and grant funding to his institution from ViiV, Gilead, Merck, Janssen, and Pfizer. C. A. B. has received payment for GSK board membership and Infectious Diseases Society of America board membership, speakers bureau, and travel and is an associate editor for Clinical Infectious Diseases; she has received grant funding to her institution from Gilead. T. W. has served as a paid consultant for ViiV/GSK and has received grant funding to his institution from ViiV/GSK, Gilead, and Bristol-Myers Squibb; his spouse holds stock options at Johnson & Johnson. S. L. K has

received grant funding to her institution from Gilead. E. P. A. reported nonfinancial support from GSK/ViiV. J. Z. L. has served as a paid consultant and received grant funding from Gilead and Merck. P. E. S. has served as a paid consultant to Gilead, Abbvie, Merck, Janssen, ViiV/GSK, and Bristol-Myers Squibb, and has received grant funding to his institution from Gilead. All other authors report no potential conflicts.

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