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Dolutegravir plus lamivudine for initial treatment of HIV-1-infected participants with HIV-1 RNA <500 000 copies/mL: week 48 outcomes from ACTG 5353

Amesika N. Nyaku [1]*, Lu Zheng[2], Roy M. Gulick[3], Maxine Olefsky[2], Baiba Berzins[4], Carole L. Wallis[5], Catherine Godfrey[6], Paul E. Sax[7], Edward P. Acosta[8], David W. Haas[9,10], Kimberly Y. Smith[11], Beverly E. Sha[12], Cornelius N. Van Dam[13] and Babafemi O. Taiwo[4] on behalf of the ACTG A5353 Study Team†

[1]Rutgers University, Newark, NJ, USA; [2]Harvard T. H. Chan School of Public Health, Boston, MA, USA; [3]Weill Cornell Medical College, New York, NY, USA; [4]Northwestern University, Chicago, IL, USA; [5]BARC-SA and Lancet Laboratories, Johannesburg, South Africa; [6]Division of AIDS, National Institutes of Allergy and Infectious Diseases, Bethesda, MD, USA; [7]Brigham and Women's Hospital, Boston, MA, USA; [8]University of Alabama, Birmingham, AL, USA; [9]Vanderbilt University, Nashville, TN, USA; [10]Meharry Medical College, Nashville, TN, USA; [11]ViiV Healthcare, Research Triangle Park, NC, USA; [12]Rush University Medical Center, Chicago, IL, USA; [13]Regional Center for Infectious Diseases, Cone Health, Greensboro, NC, USA

*Corresponding author. 185 South Orange Ave, MSB I 689, Newark, NJ 07103, USA. Tel: +1 973 972 6214; Fax: +1 973 972 1141;
E-mail: amesika.nyaku@rutgers.edu orcid.org/0000-0002-1703-0500
†Other members are listed in the Acknowledgements section.

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Background: The AIDS Clinical Trials Group study A5353 demonstrated the efficacy and safety of dolutegravir and lamivudine for initial treatment of HIV-1 infection at week 24 in individuals with HIV-1 RNA 1000–500 000 copies/mL. Optimal ART for treatment-naive individuals must be durable.

Objectives: The aim of this study was to estimate the efficacy and safety of dolutegravir plus lamivudine at week 48 and compare the efficacy in participants with baseline HIV-1 RNA ≤100 000 copies/mL versus >100 000 copies/mL.

Methods: Virological success was defined as HIV-1 RNA <50 copies/mL by FDA Snapshot criteria. Definition of virological failure included confirmed HIV-1 RNA >200 copies/mL at week 24 or later. The proportion of participants with virological success was estimated using two-sided exact Clopper–Pearson 95% CI. Comparison between screening HIV-1 RNA (≤100 000 versus >100 000 copies/mL) strata was carried out by Fisher's exact test. The study was registered with ClinicalTrials.gov, number NCT02582684.

Results: A total of 120 enrolled eligible participants were included in the analysis. At week 48, 102 of the 120 participants (85%; 95% CI 77%–91%) had virological success. Virological success was similar between screening HIV-1 RNA groups. Six (5%) participants had virological non-success and one additional participant experienced virological failure while on study but off study treatment. No new drug resistance mutations were observed. Six (5%) participants had study-related grade 3 or higher adverse events and none discontinued study treatment.

Conclusions: These results add to the evidence that dolutegravir plus lamivudine is a safe and effective option for initial ART in individuals with HIV-1 RNA <500 000 copies/mL.

Introduction

Optimal ART for treatment-naive individuals must be safe, effective and durable. Although three-drug regimens are standard, recent preliminary data suggest that two-drug regimens may be safe and effective.[1,2] In the pilot ACTG A5353 study, dolutegravir plus lamivudine was safe and efficacious through to week 24 in treatment-naive participants with a screening plasma HIV-1 RNA of 1000–500 000 copies/mL, with similar virological responses in those with a baseline HIV-1 RNA of ≤100 000 copies/mL or >100 000 copies/mL.[2] The PADDLE study, which restricted baseline HIV-1 RNA to ≤100 000 copies/mL and CD4+ T cell (CD4) count to ≥200 cells/mm^3, provided preliminary evidence of the durability of dolutegravir plus lamivudine treatment through week 96.[3] Here we present the durability of dolutegravir plus lamivudine, through week 48, in the population investigated in A5353.

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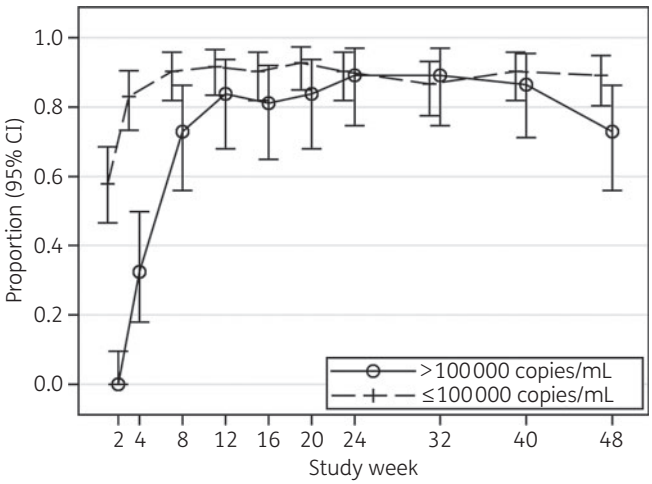

Figure 1. Proportion (95% CI) of participants with HIV-1 RNA <50 copies/mL by week (ITT/missing = failure).

Patients and methods

The complete A5353 study procedures are described in the week 24 primary report.[2] Briefly, A5353 was a single-arm, open-label, phase II study in which treatment-naive adults with HIV-1 RNA <500 000 copies/mL and no reverse transcriptase, integrase or major protease resistance mutations, as defined by the IAS-USA HIV Drug Resistance Mutation List,[4] received oral dolutegravir 50 mg and lamivudine 300 mg as separate tablets (ViiV Healthcare, Brentford, UK) once daily. There was no CD4 count eligibility criterion. Enrolment of at least 25% of participants with baseline HIV-1 RNA >100 000 copies/mL was pre-specified. During 52 weeks of follow-up, participants underwent clinical evaluations and laboratory safety, lipid, HIV-1 RNA and CD4 count measurements, as well as adherence assessments by self-reported 4 day recall.[5] Real-time HIV-1 drug resistance testing was performed in participants with confirmed virological failure along with retrospective testing of dolutegravir plasma levels if the viral failure occurred on study treatment.

This report focuses on the secondary study objectives of virological success, safety assessments, and changes in CD4 count and serum lipids at week 48. Virological success was defined as HIV-1 RNA <50 copies/mL by FDA Snapshot criteria. Protocol-defined virological failure was confirmed HIV-1 RNA >400 copies/mL at week 16 or 20, or >200 copies/mL at week 24 or later. The proportion of participants with virological success was estimated using two-sided exact Clopper–Pearson 95% CI. Comparison between baseline HIV-1 RNA strata (≤100 000 versus >100 000 copies/mL) was carried out by Fisher's exact test. All *P* values were nominal, with no adjustment for multiple comparisons. All analyses were carried out using Statistical Analysis System (SAS), version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

The local institutional review boards approved the study at each of the sites, and each participant provided written informed consent. The study was registered with ClinicalTrials.gov, number NCT02582684.

Results

The study enrolled 120 eligible participants, 87% were male with a median age of 30 years (IQR 24–41), and was racially diverse (40% black and 27% Latino). The median (IQR) baseline HIV-1 RNA was 4.61 (3.94–5.05) $\log_{10}$ copies/mL and 37 (31%) participants had baseline HIV-1 RNA >100 000 copies/mL. The median (IQR) CD4 count was 387 (288–596) cells/mm^3. One hundred (83%) participants completed study treatment per protocol whereas 20 (17%) prematurely discontinued the study treatment owing to inability to attend the clinic visits ($n = 8$), loss to follow-up ($n = 7$), non-compliance with treatment ($n = 3$), pregnancy ($n = 1$) or virological failure ($n = 1$).

At week 48, 102 of the 120 participants (85%; 95% CI 77%–91%) had virological success by FDA Snapshot (Table 1). Virological success by baseline HIV-1 RNA stratum was similar with 29/37 participants (78%; 95% CI 62%–90%) in the >100 000 copies/mL stratum and 73/83 participants (88%; 95% CI 79%–94%) in the ≤100 000 copies/mL stratum achieving HIV-1 RNA <50 copies/mL ($P = 0.18$). Using an ITT missing/off treatment = failure approach (ITT-F), 101 of the 120 participants (84%; 95% CI 76%–90%) achieved HIV-1 RNA <50 copies/mL with no significant differences between the two baseline HIV-1 RNA strata (Figure 1). Using an as-treated approach, 101 of the 104 (97%; 95% CI 92%–99%) achieved HIV-1 RNA <50 copies/mL, similarly with no significant differences between the HIV-1 RNA strata. At every visit, 87% or more of participants reported no missed doses in the four preceding days.

Six (5%) participants had virological non-success (HIV-1 RNA ≥50 copies/mL) at week 48. Two of these participants were on study treatment, one discontinued study treatment early and three were lost to follow-up/deemed non-adherent by site investigators. All of these participants had HIV-1 RNA <50 copies/mL at one or more timepoints in the first 20 weeks of treatment, prior to virological rebound. Twelve (10%) participants did not have virological data during the week 48 visit evaluation window. Three of these participants had missing data and nine had discontinued study treatment due to loss to follow-up or pregnancy, all with HIV-1 RNA <50 copies/mL at the last available timepoint. In addition to the three participants who experienced protocol-defined virological failure by week 24,[2] one participant had virological failure after week 24. This participant achieved HIV-1 RNA <50 copies/mL by week 8 and was found to be pregnant at study week 20 (~5 weeks post-conception). The participant's HIV-1 RNA was <50 copies/mL and she was switched to raltegravir and tenofovir disoproxil fumarate/emtricitabine. The participant was non-adherent to the new regimen and virological failure occurred at study week 33 with an HIV-1 RNA of 5459 copies/mL. No reverse transcriptase or integrase region resistance mutations were detected. She remained viraemic through the remainder of her pregnancy despite further ART modification, and delivered at 37 weeks, via elective caesarean section, an HIV-negative girl with an ectopic kidney.

Sixteen (13.3%) participants experienced Grade 3 or greater adverse events which the site investigator categorized as related or possibly related to study treatment in 6 (5%) participants: change in creatinine clearance ($n = 2$), and one each of angio-oedema, paraesthesia, palpitations and suicidal ideation. There was no premature discontinuation of study treatment or study follow-up due to an adverse event.

Among all participants, the median CD4 count increased by 182 (IQR 104–284) cells/mm^3 whereas the median calculated creatinine clearance decreased by 10 (IQR −18 to 2) mL/min. The median

Table 1. Virological outcomes by US FDA Snapshot at week 48

	Baseline HIV-1 RNA (copies/mL)		
	>100 000 (*N* = 37)	≤100 000 (*N* = 83)	Total (*N* = 120)
Virological success[a], *n* (%)	29 (78)	73 (88)	102 (85)
Virological success[a], 95% CI	62%–90%	79%–94%	77%–91%
Virological non-success, *n* (%)	3 (8)	3 (4)	6 (5)
HIV-1 RNA ≥50 copies/mL	1	1	2
Discontinued for lack of efficacy; HIV-1 RNA ≥50 copies/mL	1	0	1
Discontinued study treatment for other reasons[b] while HIV-1 RNA ≥50 copies/mL	1	2	3
No virological data in window, *n* (%)	5 (14)	7 (8)	12 (10)
On study but missing data in window	3	0	3
Discontinued study treatment for other reasons[c]	2	7	9

The confidence intervals in the table are exact binomial 95% CIs.
[a]HIV-1 RNA <50 copies/mL.
[b]Lost to follow-up, poor adherence.
[c]Lost to follow-up, pregnancy.

changes in lipids were total cholesterol +10 (IQR −6 to 24) mg/dL, LDL cholesterol +3.5 (IQR −11 to 6) mg/dL and HDL cholesterol +6 (IQR 1–11) mg/dL, whereas there was no change in triglyceride levels (0, IQR −27 to 26 mg/dL).

Discussion

Although dolutegravir plus lamivudine demonstrated promising safety and efficacy at week 24 in ART-naive participants with screening plasma HIV RNA <500 000 copies/mL,[2] week 48 is the standard timepoint for comparative evaluation of the safety, efficacy and durability of initial ART. Thus at week 48, virological success (HIV-1 RNA <50 copies/mL by the FDA Snapshot criterion) was achieved in 85% of participants treated with dolutegravir plus lamivudine, with no significant differences between those whose pre-treatment HIV-1 RNA was above or below 100 000 copies/mL. These results were consistent in ITT, missing/off treatment = failure and as-treated analyses. These results were similar to the findings of larger, fully powered, randomized clinical trials. The week 48 efficacy of the US Department of Health and Human Services guideline-recommended bictegravir-, dolutegravir-, elvitegravir/cobicistat- or raltegravir-based three-drug regimens ranged from 86.1% to 92.4%.[6–12]

It is reassuring that only one participant had virological failure between weeks 24 and 48 on dolutegravir plus lamivudine in this study. The participant was off dolutegravir plus lamivudine due to pregnancy and was on raltegravir-based three-drug therapy at the time of virological failure. There were no failures with HIV-1 drug resistance between week 24 and week 48. At week 24, as previously reported, one participant developed resistance mutations to the study drugs (R263R/K and M184V),[2] and additional virological analyses to evaluate minority variants and phenotyping are currently underway. Dolutegravir plus lamivudine was generally safe and well tolerated in this pilot study. No neural tube defects occurred in the baby that was exposed to dolutegravir in the first 5 weeks of pregnancy and, based on data from the Antiretroviral Pregnancy Registry, the renal defect was unlikely to be related to study treatment.[13–15]

Our results are limited by the relatively small sample size, the lack of a comparator arm, short follow-up period and enrolment of few women and few participants with a CD4 count <200 cells/mm^3. Nevertheless, our results agree with the pooled analysis of the ongoing fully powered phase III clinical trials, GEMINI 1 and 2. In the GEMINI studies, dolutegravir plus lamivudine was non-inferior to dolutegravir plus tenofovir disoproxil fumarate/emtricitabine at week 48 by FDA Snapshot; virological success 91% versus 93%; treatment difference −1.7% (95% CI −4.4% to 1.1%).[16] Similar to our study, women and individuals with CD4 counts <200 cells/mm^3 were under-represented in the GEMINI studies. Among participants with CD4 counts <200 cells/mm^3, viral suppression by FDA Snapshot was numerically lower with dolutegravir plus lamivudine, but was comparable between arms when failure was defined as treatment-related discontinuation. Follow-up through week 144 is planned. Like other tenofovir-free regimens, dolutegravir plus lamivudine is insufficient treatment in individuals co-infected with HBV. Additionally, the efficacy of dolutegravir plus lamivudine when administered with rifampicin in TB co-infection is unknown, and pre-treatment resistance testing is required, which will constrain its use in resource-limited settings and for same-day ART initiation.

In conclusion, the week 48 results of A5353 add to the evidence that dolutegravir plus lamivudine may be a safe and effective option for initial ART, with lower antiretroviral exposure than three-drug alternatives.

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Disclaimer

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