Impact of Treatment Adherence on Efficacy of Dolutegravir + Lamivudine and Dolutegravir + Tenofovir Disoproxil Fumarate/ Emtricitabine: Pooled Week 144 Analysis of the GEMINI-1 and GEMINI-2 Clinical Studies

***To the Editors*:**

Antiretroviral therapy (ART) for the treatment of HIV-1 must remain efficacious throughout a person's life. High adherence to ART is consistently associated with higher rates of virologic suppression, as shown in studies using thresholds of >90% or >95% for high adherence.[1] However, perfect lifetime adherence may be unrealistic, especially if the regimen has undesirable side effects[2] or a high pill burden.[1] The ability of an ART regimen to remain efficacious despite imperfect adherence, or "regimen forgiveness," is a determinant of decreasing the risk of virologic rebound and resistance development when doses are sporadically missed.[3] Forgiveness can indicate the long-term durability and potency of an ART regimen.

The randomized, controlled, phase 3 GEMINI-1 and GEMINI-2 trials (ClinicalTrials.gov, NCT02831673 and NCT02831764, respectively) demonstrated the durable efficacy of the once-daily 2-drug regimen (2DR) dolutegravir + lamivudine, with sustained noninferiority compared with the 3-drug regimen (3DR) dolutegravir + tenofovir disoproxil fumarate/emtricitabine in treatment-naive participants through 3 years.[4–6] In addition, a week 48 post hoc analysis categorizing participants from the GEMINI trials by ≥90% or <90% adherence demonstrated similar rates of virologic suppression between treatment regimens in each adherence category. Decreased adherence resulted in lower efficacy regardless of the number of drugs in the regimen, demonstrating that the impact of adherence on efficacy did not differ between the 2DR and 3DR.[7] Here, we report longer-term results by treatment adherence at week 144 in a post hoc analysis of GEMINI-1 and GEMINI-2.

Participants were randomized to once-daily 2DR or 3DR; treatment was double-blind from weeks 1 to 96 and open-label thereafter. Detailed methods of the GEMINI-1 and GEMINI-2 trials have been previously published.[4–6] In brief, the proportion of participants with HIV-1 RNA <50 copies/mL at week 144 was assessed using the US Food and Drug Administration Snapshot algorithm (missing, switch, or discontinuation = failure) and last on-treatment viral load (not accounting for discontinuations for nonvirologic reasons) for participants for whom adherence level could be derived. Adherence was determined through pill count estimates, and participants were categorized as ≥90% or <90% adherent.[7] The intention-to-treat exposed population was used for primary efficacy and post hoc adherence analyses and included all randomized participants who received ≥1 dose of study medication. The Clopper–Pearson exact method was used to calculate 95% CI for the proportion of participants with HIV-1 RNA <50 copies/mL within treatment groups in each adherence category. All protocols, amendments, and necessary study documents were reviewed and approved by an ethics committee or institutional review board in accordance with International Conference on Harmonization Good Clinical Practice guidelines and applicable country-specific requirements as appropriate. Written informed consent was obtained from all participants before initiating any study procedures.

Overall demographics and baseline characteristics have previously been published.[4] Demographics were generally balanced between treatment groups and adherence categories at week 144, except for a slightly higher proportion of participants identifying as Black/African American in the lower adherence category. Baseline HIV-1 RNA and $CD4^+$ cell count were comparable across treatment groups and adherence categories (see Table, Supplemental Digital Content, http://links.lww.com/QAI/C102, demographics and baseline characteristics). Median (interquartile range) percent adherence at week 144 was similar within adherence categories across treatment groups (Fig. 1A), and the distribution of adherence rates was similar between treatment groups (see Figure, Supplemental Digital Content, http://links.lww.com/QAI/C103, proportions of participants per adherence rate category). Adherence percentage rates for the <90% and ≥90% adherence groups were similar at the week 48 analysis. Most participants had complete pill count data to estimate adherence for dolutegravir (2DR, 620/716 [87%]; 3DR, 640/717 [89%]) and for the double-blind treatment of either lamivudine or tenofovir disoproxil fumarate/

Supported by ViiV Healthcare.

Presented at 18th European AIDS Conference; October 27–30, 2021; Virtual and London, UK; Poster PE2/63.

E.F., C.M., J.S., A.Z., B.W., J.v.W., and M.A.-K. are employees of ViiV Healthcare and own stock in GSK. N.E. has received grants from Merck; honoraria for participation in presentations or educational events from Merck, Gilead, Janssen, and GSK; and travel support from Gilead, Janssen, and GSK; and has participated in data safety monitoring or advisory boards for Merck, Gilead, and GSK. RGulminetti has received grants from Gilead and ViiV Healthcare, which were paid to his institution; received consulting fees from AbbVie, Gilead, ViiV Healthcare, and Merck Sharp & Dohme; received honoraria from Gilead, ViiV Healthcare, and Merck Sharp & Dohme; provided expert testimony for Gilead and ViiV Healthcare; and received travel support from Gilead. D.H. has served as a principal investigator through her institution, received honoraria for participation in speakers bureaus, and received travel support from GSK/ViiV Healthcare; has participated in advisory boards for ViiV Healthcare; and serves on the Georgia ADAP committee. RGrove is an employee of and owns stock in GSK. J.S.M. and H.-C.T. have no conflicts of interest to disclose.

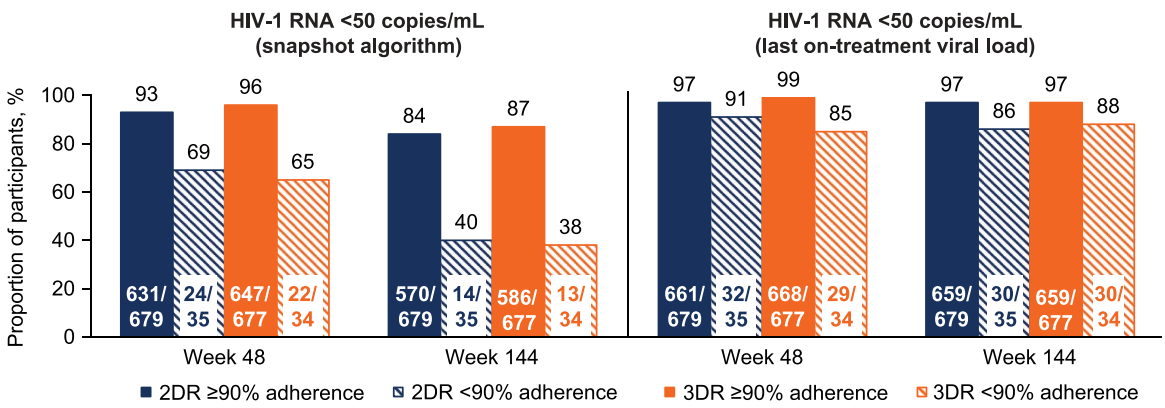
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

A

	Week 144			
	2DR (N=716)		3DR (N=717)	
Adherence results	**≥90%**	**<90%**	**≥90%**	**<90%**
Adherence category, n (%)[a]	679 (95)	35 (5)	677 (94)	34 (5)
Percent adherence rate, median (IQR)	99.6 (97.9-100.0)	85.7 (82.1-88.5)	99.5 (97.7-99.9)	84.7 (82.0-88.5)

B



C

	Week 48				Week 144			
	2DR		3DR		2DR		3DR	
Outcomes, n (%)	**≥90% (N=679)**	**<90% (N=35)**	**≥90% (N=677)**	**<90% (N=34)**	**≥90% (N=679)**	**<90% (N=35)**	**≥90% (N=677)**	**<90% (N=34)**
HIV-1 RNA <50 copies/mL	631 (93)	24 (69)	647 (96)	22 (65)	570 (84)	14 (40)	586 (87)	13 (38)
HIV-1 RNA ≥50 copies/mL	16 (2)	4 (11)	9 (1)	4 (12)	17 (3)	6 (17)	18 (3)	3 (9)
Data in window and HIV-1 RNA ≥50 copies/mL	8 (1)	0	4 (1)	1 (3)	3 (<1)	1 (3)	5 (<1)	0
Discontinued for lack of efficacy	3 (<1)	2 (6)	2 (<1)	0	7 (1)	3 (9)	4 (<1)	0
Discontinued for other reason and HIV-1 RNA ≥50 copies/mL	4 (1)	1 (3)	2 (<1)	3 (9)	6 (<1)	1 (3)	8 (1)	3 (9)
Change in ART	1 (<1)	1 (3)	1 (<1)	0	1 (<1)	1 (3)	1 (<1)	0
No virologic data	32 (5)	7 (20)	21 (3)	8 (24)	92 (14)	15 (43)	73 (11)	18 (53)
Discontinued study for AE or death	9 (1)	1 (3)	8 (1)	4 (12)	28 (4)	1 (3)	26 (4)	5 (15)
Discontinued study for other reason[b]	21 (3)	6 (17)	13 (2)	4 (12)	63 (9)	13 (37)	47 (7)	12 (35)
On study but missing data in window	2 (<1)	0	0	0	1 (<1)	1 (3)	0	1 (3)

D

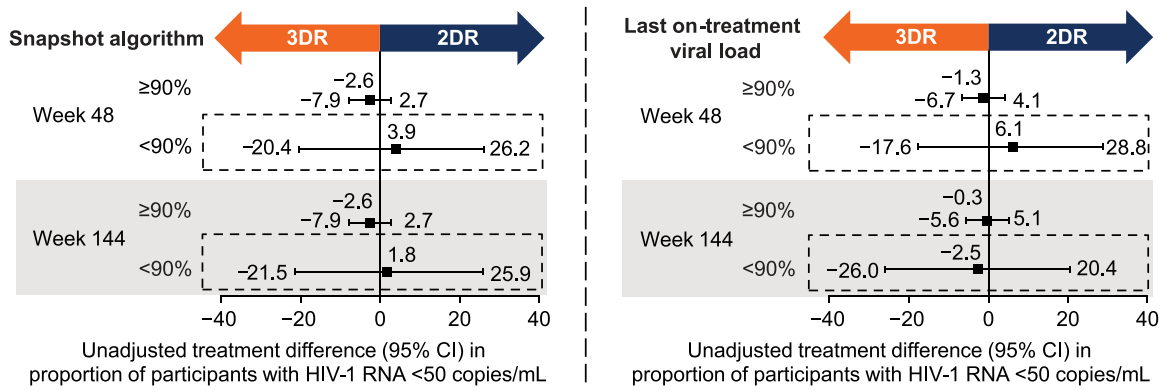


FIGURE 1. A, Week 144 adherence results in GEMINI-1 and GEMINI-2 by adherence category. B, Proportion of participants with HIV-1 RNA <50 copies/mL by adherence category using snapshot and last on-treatment viral load at weeks 48[7] and 144. C, Snapshot outcomes by adherence category at weeks 48 and 144. D, Treatment differences between proportion of participants with HIV-1 RNA <50 copies/mL by adherence category at weeks 48 and 144. All data are from the ITT-E population. AE, adverse event; IQR, interquartile range; ITT-E, intention-to-treat exposed. [a]Adherence categories only include participants with derived study drug adherence data. [b]Other reasons included lost to follow-up, investigator discretion, withdrawal of consent, and protocol deviation.

emtricitabine (2DR, 664/716 [93%]; 3DR, 671/717 [94%]).

For both treatment groups, the proportion of participants achieving HIV-1 RNA <50 copies/mL (snapshot) was lower in the <90% adherence group compared with the ≥90% adherence group at week 144, consistent with week 48 findings (Fig. 1B). As observed at week 48, in the analysis using last on-treatment viral load, a higher proportion of participants had virologic suppression at week 144 in the ≥90% vs <90% adherence category, regardless of treatment group, indicating that nonresponse by snapshot analysis was driven by nonvirologic reasons. Snapshot efficacy rates in the <90% adherence category decreased from week 48 to week 144 to a greater extent than the decrease over time in the ≥90% adherence category, mostly driven by more participants having no virologic data at week 144 in the <90% adherence category (Fig. 1C). Lower response rates observed using snapshot compared with last on-treatment viral load were driven by nonvirologic snapshot failures. The proportion of participants with no virologic data (snapshot) increased from week 48 to week 144 across both treatment groups.

The unadjusted difference in proportion of participants who achieved virologic suppression at week 144 between the 2DR and 3DR treatment groups was similar based on snapshot analysis and last on-treatment viral load (Fig. 1D).

DISCUSSION

Similar rates of virologic suppression were observed between 2-drug and 3-drug dolutegravir-based regimens regardless of treatment adherence category through 3 years of treatment in the GEMINI-1 and GEMINI-2 trials. As expected, virologic suppression rates were lower when adherence was <90% vs ≥90% for both treatment groups. As observed at week 48, virologic response rates in each adherence category were high by last on-treatment viral load analysis regardless of treatment regimen at week 144; however, slightly lower rates were observed in those with <90% vs ≥90% adherence. Response rates in the <90% adherence category for both treatment groups were higher in last on-treatment viral load vs snapshot analyses, with the difference mostly driven by nonvirologic reasons such as lost to follow-up and withdrawal of consent. Unlike in vitro findings that suggest that different integrase inhibitor–based regimens have varying levels of regimen forgiveness,[8] clinical evidence from this study indicates that lower adherence reduces virologic efficacy to the same extent regardless of regimen and highlights the importance of interpreting in vitro data with caution, especially when superseded by clinical data. This is consistent with the randomized controlled GS-US-380-1489 trial comparing the 3DRs bictegravir/tenofovir alafenamide/emtricitabine with dolutegravir/abacavir/lamivudine, which reported similar efficacy outcomes among participants using more stringent ≥95% or <95% adherence thresholds assessed using pill count.[9]

A similar proportion of participants across adherence levels withdrew because of adverse events or death. Most of the participants with <90% adherence withdrew for nonvirologic reasons in both the week 48[7] and week 144 analyses, suggesting that participants with lower adherence have higher attrition in the long-term trial and were either lost to follow-up or withdrew consent. Ensuring that people living with HIV are satisfied with their ART may improve adherence;[10] however, treatment satisfaction and other parameters potentially associated with adherence are not always measured in randomized clinical trials. This highlights the need for further studies to translate adherence factors from clinical trials to real-world practice.

One limitation of this analysis is that the postbaseline categorization of participants into <90% and ≥90% adherence groups at week 144 may confound the correlation between adherence and efficacy. Another limitation is the small sample size of the <90% adherence group. In addition, pill counts may not accurately reflect participant adherence if medication is missing or discarded; however, pill count is a common clinical trial adherence measure and correlates highly with other adherence measures.[11] The strength of this analysis is the randomization, which limits any baseline confounders in the comparison between treatment groups as well as the long-term follow-up over 3 years. In the analysis using last on-treatment viral load, the impact of lower adherence on efficacy at the week 48 and week 144 time points was consistent between treatment regimens, indicating that lower adherence over a longer period of time does not negatively affect the efficacy of 2DR relative to 3DR. Furthermore, the lower efficacy observed using snapshot analysis in participants with <90% adherence was similar between treatment groups, also showing a similar impact of adherence on efficacy regardless of 2DR relative to 3DR. These data confirm prior published data and support that high adherence levels quantified using pill count are associated with improved rates of virologic suppression.[1] Data concerning the exact times of missed doses were not recorded, which may have affected efficacy results if one or more doses were consecutively missed immediately before viral loads were measured. This precludes estimating adherence levels in relation to confirmed virologic failure; in GEMINI-1/-2, similar numbers of confirmed virologic failures occurred in each treatment group and no treatment-emergent resistance mutations were observed. Although drug plasma concentrations were not measured in the GEMINI trials, the pharmacokinetic profiles of dolutegravir and lamivudine sufficiently afford synergistic pharmacokinetic protection beyond a single missed dose.[12]

In conclusion, lower adherence was associated with lower rates of virologic suppression at week 144 regardless of treatment group, consistent with 48-week findings.[7] These results suggest that the 2DR dolutegravir + lamivudine has similar forgiveness with imperfect adherence as the 3DR dolutegravir + tenofovir disoproxil fumarate/emtricitabine; however, clinicians should continue to advocate for optimal adherence (ie, "every dose, every day") to support people living with HIV-1 in achieving and maintaining virologic suppression to decrease the risks of virologic rebound, HIV-1 transmission, and resistance development.

ACKNOWLEDGMENTS

The authors thank the study participants; their families and caregivers; the investigators and site staff who participated in the study; and the ViiV Healthcare, GSK, Pharmaceutical

Product Development, and Parexel study team members. Editorial assistance was provided under the direction of the authors by Lindsay Walton, PhD, and Jennifer Rossi, MA, ELS, MedThink SciCom, and funded by ViiV Healthcare.

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