INITIAL SUPPLEMENTAL DOLUTEGRAVIR DOSE IN SECOND-LINE ART: A PHASE 2 RANDOMISED TRIAL

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BACKGROUND

Dolutegravir concentrations are reduced by the induction effect of efavirenz, necessitating twice daily dolutegravir dosing when co-administered. Efavirenz induction persists for several weeks after stopping, which could select for resistance if switching occurred with unsuppressed HIV-1 RNA levels. We evaluated the need for a lead-in supplemental dolutegravir dose in adults failing first-line antiretroviral therapy (ART) with tenofovir-emtricitabine-efavirenz (TEE) switching to tenofovir-lamivudine-dolutegravir (TLD).

METHODS

- We conducted a randomised, double-blind, placebo-controlled, phase 2 trial in Khayelitsha, Cape Town, South Africa.
- Eligible patients had virologic failure (defined as two consecutive plasma HIV-1 RNA ≥1000 copies/mL) on first-line TEE.
- Participants were randomly assigned (1:1) to switch to TLD with a supplemental 50 mg dolutegravir dose or placebo taken 12 hours later for 14 days.
- The primary outcome was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at week 24.
- This study was not powered to formally compare arms.

Table 1: Baseline characteristics

Variable	TLD + DTG (N = 65)	TLD + Placebo (N = 65)
Age, years – median (IQR)	38 (33 – 45)	39 (34 – 45)
Female sex – no. (%)	42 (65)	47 (72)
CD4+ cell count, cells/mm^3 – median (IQR)	246 (187 – 334)	250 (154 – 349)
HIV-1 RNA, $\log_{10}$ copies/mL – median (IQR)	4.12 (3.46 – 4.69)	4.01 (3.51 – 4.66)
Time receiving first-line ART, months – median (IQR)	77 (45 – 112)	93 (57 – 132)
Previously received stavudine or zidovudine – no. (%)	4 (6)	12 (18)
NRTI genotypic resistance* – no./N (%)		
Two fully active NRTIs	2/63 (3)	2/57 (4)
Resistance to one NRTI	15/63 (24)	10/57 (18)
Tenofovir, not XTC	0/63 (0)	0/57 (0)
XTC, not tenofovir	15/63 (24)	10/57 (18)
Resistance to both NRTIs	46/63 (73)	45/57 (79)
Efavirenz genotypic resistance* – no./N (%)	63/63 (100)	57/57 (100)

*Resistance was classified with the Stanford algorithm, with a score of ≥15 indicating at least low-level resistance.

Among adults switching to second-line TLD with unsuppressed HIV-1 RNA levels and substantial baseline NRTI resistance, a high proportion achieved virologic suppression. Our findings do not support a lead-in supplemental dolutegravir dose to overcome efavirenz induction effect when switching to second-line TLD.

RESULTS

- 130 participants were randomly assigned to receive TLD with supplemental dolutegravir (n = 65) or placebo (n = 65) (**Figure 1**).
- Baseline characteristics were similar between arms (**Table 1**).
- At week 24, 55/64 (86%) in the supplemental dolutegravir arm and 53/65 (82%) in the placebo arm had HIV-1 RNA <50 copies/mL (**Table 2**).
- Time to virologic suppression by arm is shown in **Figure 2**.
- In the subgroup of participants with baseline resistance to both tenofovir and lamivudine, 76 (84%) of 90 participants had HIV-1 RNA <50 copies/mL at week 24 across both arms.
- Grade 3 or 4 adverse events were similar in frequency between arms.
- At 2 weeks, 8 (12%) participants in the supplemental dolutegravir arm and 9 (14%) participants in the placebo arm reported insomnia as an adverse event and had a ≥1 ISI score change from baseline, with rapid attenuation of symptoms and ISI scores over time.
- None of the six participants (3 in each arm) meeting criteria for resistance testing developed dolutegravir resistance over 24 weeks.

Table 2: Summary of primary and certain secondary efficacy outcomes

Variable	HIV-1 RNA <50 copies/mL (n, % [95% CI])		HIV-1 RNA <400 copies/mL (n, % [95% CI])	
	TLD + DTG (N = 65)	TLD + Placebo (N = 65)	TLD + DTG (N = 65)	TLD + Placebo (N = 65)
Week 24				
mITT analysis[a]	55/64 (86% [75 – 93])	53/65 (82% [70 – 90])	63/64 (98% [92 – 100])	59/65 (91% [81 – 97])
Sensitivity analysis[b]	55/64 (86% [75 – 93])	53/61 (87% [76 – 94])	63/64 (98% [92 – 100])	59/61 (97% [89 – 100])

[a]Modified intention-to-treat (mITT) analysis excludes death from non-HIV and non-drug causes.

[b]Sensitivity analysis excludes those excluded from mITT analysis, as well as loss to follow up, missing VL within the window, switching study drug for reasons other than treatment failure, and evidence of poor adherence (TFV-DP <350 fmol/punch).

CONCLUSIONS

- TLD in second-line ART was effective and well tolerated in both arms. Our findings do not support the need for initial dolutegravir dose adjustment in patients switching to TLD who failed first-line TEE.

ADDITIONAL KEY INFORMATION

- We have no conflicts of interest to disclose.
- This work was supported by the Wellcome Trust through an investigator award (212265/Z/18/Z) and core funding from the Wellcome Centre for Infectious Diseases Research in Africa (203135/Z/16/Z).

Figure 1: Participant flow diagram

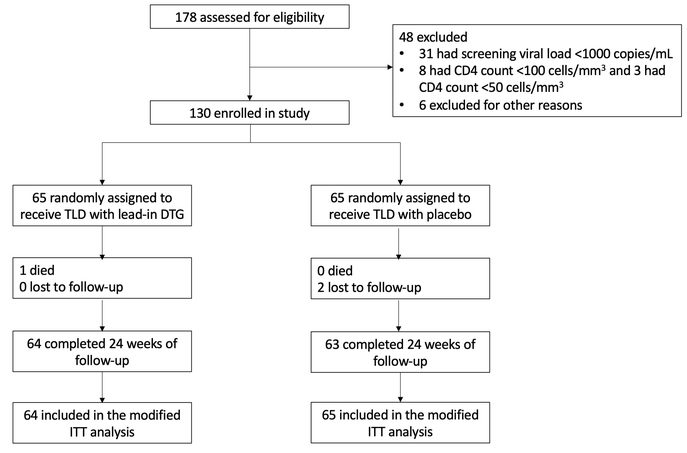


Figure 2: Kaplan-Meier for time to virological suppression

