Pharmacokinetics of Standard vs Double-dose Dolutegravir after Switch from Efavirenz

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Background

- The WHO recommends dolutegravir as preferred second-line antiretroviral therapy (ART) agent for people with HIV (PWH). (1)
- Efavirenz is a potent inducer of genes involved in the metabolism and transport of dolutegravir. (2)
- Dolutegravir concentrations are reduced for several weeks after switching from efavirenz- to dolutegravir-based ART but outcomes are good among virologically suppressed PWH. (3,4)
- In people switching from failing efavirenz-based ART to dolutegravir-based ART, exposure to sub-therapeutic dolutegravir concentrations could select for integrase strand transfer inhibitor (InSTI) resistance mutations due to the high likelihood of baseline reverse transcriptase inhibitor resistance mutations.
- We aimed to evaluate the trough concentrations (C_{min}) of dolutegravir when switching from failing efavirenz-based first-line ART to assess the pharmacokinetic need for a lead-in supplemental dose of dolutegravir.
- We also assessed the effect of efavirenz metaboliser genotype on dolutegravir exposure after switching from efavirenz.

Methods

Participants and study design

- We conducted a pharmacokinetic sub-study nested in the ARTIST (clinicaltrials.gov; NCT03991013) trial. (5)
- ARTIST enrolled adults failing a first-line regimen of tenofovir, emtricitabine or lamivudine, and efavirenz or nevirapine and switched them to a second-line regimen of tenofovir, lamivudine, and dolutegravir (TLD).
- ARTIST was conducted in two stages: in stage 1 all participants received a lead-in 14 day supplemental 50 mg dolutegravir dose 12 hours later and in stage 2 participants were randomised to a lead-in 14 day supplemental dose or matching placebo 12 hours later.
- ARTIST was conducted at a community health clinic in Khayelitsha, Cape Town, South Africa.
- nclusion criteria for the pharmacokinetic sub-study:
  - consented to participation,
  - detectable baseline efavirenz concentrations confirming exposure.
- Follow-up visits occurred at days 3, 7, 14, and 28.
- Pharmacokinetic samples were taken for random efavirenz concentrations at days 3, 7, and 14 and for dolutegravir C_{min} at days 3, 7, 14, and 28.

Statistical analysis

- Dolutegravir C_{min} reported as geometric mean (GM) with 90% CI.
- Within-subject changes in dolutegravir C_{min} between days 3, 7, 14 and day 28 evaluated by calculating GM ratios (GMRs) with 90% CI.
- Univariable and multivariable linear regression models developed to assess associations between a *priori* selected variables (sex, baseline weight, log transformed efavirenz concentrations, and efavirenz metaboliser genotype) and dolutegravir C_{min} at days 3, 7, 14, and 28.
- Findings were stratified by participants receiving a lead-in supplemental 50 mg dolutegravir dose (double-dose group) or placebo (standard-dose group) for the first 14 days post-switch.
- Primary outcome: GMR of dolutegravir C_{min} on day 7 versus day 28.
- Secondary outcomes:
  - GMR of dolutegravir C_{min} on days 3 and 14 versus day 28
  - dolutegravir C_{min} below the PA-IC_{90} of 0.064 µg/mL at days 3, 7, 14 and 28

- **All participants on standard dose dolutegravir had trough concentrations above the PA-IC_{90} (0.064 µg/mL) and the geometric mean was above 0.300 µg/mL at all timepoints.**
- **Participants with slow efavirenz metaboliser genotypes had higher baseline efavirenz concentrations with more pronounced and longer duration of induction post-switch.**

Results

Participants

- We enrolled 12 participants from ARTIST stage 1 and 24 participants from ARTIST stage 2: 25 in the double-dose group and 11 in the standard-dose group.
- One participant in the double-dose group had a baseline efavirenz concentration below the lower limit of quantification and was excluded.
- The baseline characteristics of all included participants are shown in **Table 1**.
- Classification of participants by efavirenz metaboliser genotype are shown in **Table 1** (no participants in the standard-dose group had slow efavirenz metaboliser genotypes).

Table 1:
Baseline characteristics

	Double-dose group (n=24)	Standard-dose group (n=11)
Age (years), median (IQR)	36.5 (31 to 43)	34 (26 to 40)
Sex (women), n (%)	19 (79.2)	8 (72.7)
Race (black), n (%)	24 (100)	11 (100)
BMI (kg/m2), median (IQR)	31.6 (23.0 to 36.1)	26.6 (24.8 to 30.8)
CD4 count (cells/µL), median (IQR)	202 (151 to 306)	373 (260 to 523)
HIV-1 RNA (log10), median (IQR)	4.2 (3.6 to 4.5)	3.2 (3.1 to 4.1)
INH preventative therapy, n (%)	18 (75)	7 (63.6)
Cotrimoxazole preventative therapy, n (%)	6 (25)	0 (0)
Efavirenz metaboliser genotype		
Normal, n (%)	7 (29)	5 (45)
Intermediate, n (%)	12 (50)	6 (55)
Slow, n (%)	5 (21)	0 (0)

Efavirenz Pharmacokinetics

- Efavirenz concentrations over time are presented in **Figure 1**.
- In the double-dose group efavirenz concentrations were significantly higher at day 14 among the slow efavirenz metabolisers (median 0.901 µg/mL, interquartile range [IQR] 0.514 to 1.520), than the intermediate (median 0.261 µg/mL, IQR 0.065 to 0.515) or normal efavirenz metabolisers (median 0.149 µg/mL, IQR 0.134 to 0.247) (Kruskal-Wallis p=0.015) **(Figure 2)**.

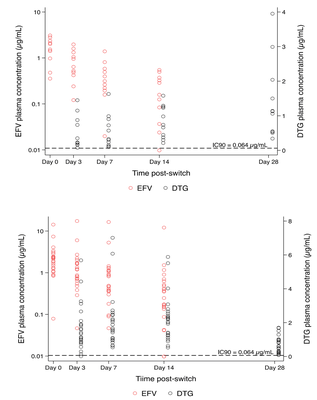

Figure 1:
Scatter plot of efavirenz and dolutegravir C_{min} post-switch from efavirenz among participants in the standard-dose (A) and double-dose (B) groups. The black dashed horizontal line represents dolutegravir PA-IC_{90}.

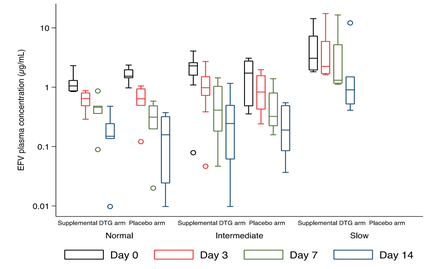

Figure 2:
Efavirenz concentrations by metaboliser genotype and group.

Dolutegravir Pharmacokinetics

- Dolutegravir C_{min} over time are presented in **Figure 1**.
- One participant in the double-dose group had a dolutegravir C_{min} below the PA-IC_{90} (0.064 µg/mL) at day 3.
- The GMs and GMRs of dolutegravir C_{min} are presented in **Table 2**.
- Dolutegravir C_{min} at day 28 differed significantly by group (Wilcoxon rank-sum p=0.026), but these were similar when stratified by efavirenz metaboliser genotypes (normal efavirenz metabolisers p=0.088 and intermediate efavirenz metabolisers p=0.223) **(Figure 3)**.

Table 2:
Geometric means and geometric mean ratios of dolutegravir C_{min} (µg/mL) by group

	Geometric Mean (90% CI)			Geometric Mean Ratio (90% CI)			
Dosing regimen	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 3/ Day 28**	**Day 7/ Day 28**	**Day 14/ Day 28**
Standard-dose group (n=11)	0.631 (0.513 to 0.777)	0.661 (0.539 to 0.809)	0.850 (0.733 to 0.986)	1.037 (0.869 to 1.237)	0.609** (0.462 to 0.802)	0.637* (0.485 to 0.837)	0.820 (0.650 to 1.035)
Double-dose group (n=24)	1.043 (0.870 to 1.250)	1.247 (0.129 to 1.378)[a]	1.315 (1.203 to 1.438)	0.754 (0.663 to 0.858)[b]	1.383* (1.106 to 1.730)	1.654 *** (1.404 to 1.948)	1.744*** (1.490 to 2.041)

* = P <0.10; ** = P <0.01; *** = P <0.001
[a] One value missing at day 7 in the double-dose group
[b] One value missing at day 28 in the double-dose group

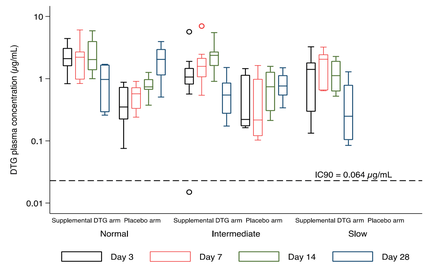

Figure 3:
Dolutegravir C_{min} by efavirenz metaboliser genotype and group

On linear regression baseline efavirenz concentrations, but not efavirenz metaboliser genotype, were independently associated with lower dolutegravir C_{min} when adjusting for weight and sex in the double-dose group and standard-dose group at days 3 (p=0.035 and p=0.029, respectively) and 7 (p=0.014 and p=0.019, respectively), and in the double-dose group at day 14 (p=0.010) **(Table 3)**.

Table 3:
Multivariable linear regression to assess effect of covariates on dolutegravir C_{min}.

	Double-dose group (n=24)		Standard-dose group (n=11)	
Covariate	**Multivariable associations**		**Multivariable associations**	
	Estimate (95% CI)	**p-value**	**Estimate (95% CI)**	**p-value**
Day 3				
Sex				
Female	Referent group		Referent group	
Male	0.078 (-0.552 to 0.709)	0.798	0.044 (-0.595 to 0.507)	0.855
Weight (per 5 kg increase)	-0.030 (-0.094 to 0.033)	0.329	0.022 (-0.041 to 0.084)	0.442
Baseline EFV concentration (per 1 log10 µg/mL increase)	**-0.590 (-1.134 to -0.045)**	**0.035**	**-1.059 (-1.970 to -0.147)**	**0.029**
Day 7[a]				
Sex				
Female	Referent group		Referent group	
Male	-0.071 (-0.401 to 0.258)	0.655	0.303 (-0.210 to 0.815)	0.205
Weight (per 5 kg increase)	-0.008 (-0.041 to 0.025)	0.615	-0.006 (-0.052 to 0.065)	0.807
Baseline EFV concentration (per 1 log10 µg/mL increase)	**-0.373 (-0.662 to -0.083)**	**0.014**	**-1.082 (-1.931 to -0.235)**	**0.019**
Day 14				
Sex				
Female	Referent group		Referent group	
Male	-0.178 (-0.460 to 0.105)	0.204	0.034 (-0.476 to 0.523)	0.881
Weight (per 5 kg increase)	-0.011 (-0.040 to 0.017)	0.414	0.002 (-0.056 to 0.060)	0.924
Baseline EFV concentration (per 1 log10 µg/mL increase)	**-0.333 (-0.577 to -0.089)**	**0.010**	-0.515 (-1.358 to 0.327)	0.191
Day 28[b]				
Sex				
Female	Referent group		Referent group	
Male	-0.262 (-0.717 to 0.193)	0.243	0.285 (-0.335 to 0.906)	0.313
Weight (per 5 kg increase)	-0.039 (-0.086 to 0.008)	0.096	-0.001 (-0.072 to 0.070)	0.971
Baseline EFV concentration (per 1 log10 µg/mL increase)	-0.320 (-0.694 to 0.054)	0.089	-0.324 (-1.350 to 0.703)	0.480

[a] One dolutegravir trough concentration and one efavirenz concentration missing in the double-dose group at day 7
[b] One dolutegravir trough concentration missing in the double-dose group at day 28

Conclusions

- Ours is the first pharmacokinetic study to explore the need for a 14-day lead in upplemental dolutegravir dose when switching from failing first-line efavirenz-based ART to second-line dolutegravir-based ART.
- No participants on standard dose dolutegravir had dolutegravir C_{min} below the PA-IC_{90} and GM was above 0.300 µg/mL at all timepoints.
- Slow efavirenz metaboliser genotypes had higher baseline efavirenz concentrations and caused a more pronounced and longer period of induction post-switch.
- These findings, in conjunction with the similar virological suppression rates between the supplemental and placebo arms from the ARTIST stage 2 trial, (6) suggest that a 14-day lead-in supplemental dolutegravir dose may not be necessary when switching from a failing efavirenz-based first-line regimen.

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