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

Rulan Griesel1,2, Clifford Banda1, Ying Zhao3, Zayid Omar2, Lubbe Wiesner1, Graeme Meintjes2,3, Phumla Sinxadi1, Gary Martens1,2

1. Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa
2. Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa
3. Department of Medicine, University of Cape Town, Cape Town, South Africa

Background
- The WHO recommends dolutegravir as preferred second-line antiretroviral therapy (ART) agent for people with HIV (PWHA).
- Efavirenz is a potent inducer of genes involved in the metabolism and transport of dolutegravir.
- Dolutegravir concentrations are reduced for several weeks after switching from efavirenz to dolutegravir-based ART but outcomes are good among virologically suppressed PWHA.

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 dolutegravir (TLD).
  - ARTIST was conducted in two stages: in stage 1 all participants received a lead-in 14 day supplemental dose or matching placebo 12 hours later.
  - 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.
  - Cotrimoxazole preventative therapy, median (IQR) 18 (75) vs 7 (63.6).

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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**
  - Participants in the standard-dose group had slow efavirenz metaboliser genotypes and participants in the double-dose group were slow and intermediate metabolisers.

- **Efavirenz Pharmacokinetics**
  - Efavirenz pharmacokinetics are over time in Figure 1.
  - In the double-dose group efavirenz concentrations were significantly higher at day 14 among slow efavirenz metabolisers (median 0.907 μg/mL, interquartile range [IQR] 0.514 to 1.529), 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<0.016) (Figure 2).

- **Dolutegravir Pharmacokinetics**
  - Dolutegravir concentrations post-switch from efavirenz.
  - One participant in the double-dose group had a dolutegravir Cmin below the PA-IC90 at day 7.
  - The concentrations and geometric mean ratios of dolutegravir Cmin over time are presented in Figure 2.

Conclusions
- Dolutegravir was the first pharmacokinetic study to explore the need for a 14-day lead in supplemental dolutegravir dose when switching from failing first-line efavirenz-based ART to second-line dolutegravir-based ART.
- Participants with slow efavirenz metaboliser genotypes had baseline efavirenz concentrations and post-switch dolutegravir concentrations.

All participants on standard dose dolutegravir had trough concentrations above the PA-IC90 (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.

References
6. Zhao Y, et al. Pharmacological sub-study participants in the ARTIST (clinicaltrials.gov; NCT03991013) trial. (5)

Author contacting information
Dr. Rulan Griesel, Email: rulan.griesel@uct.ac.za
Professor Clifford Banda, Email: cliff-band@uct.ac.za
Department of Medicine, University of Cape Town, Cape Town, South Africa

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