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9th SA TB Conference
8 – 11 June 2026

Simplifying TB-HIV Co-infection treatment in children with HIV ORCHID study

Session: Optimising TB outcomes in adults and children

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09 June 2026

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CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

Background

- **Co-treatment of HIV and TB** in children is virtually unavoidable in high-endemic areas of Africa, yet options for this vulnerable population remain extremely limited.

- DTG-based regimen in children (>3kg and > 4weeks), adolescents, and adults, is now standard-of-care therapy for HIV, so it is critically important to know how to dose children who also have TB.

- The WHO has recently included **DTG BD dosing** when co-administered with RIF in children based on extrapolation from adult data. This approach needs supporting data with an adequate number of children across age and weight bands.

Adult data supporting once daily DTG

- A phase 2b, non-comparative, placebo-controlled, randomised trial showed that DTG 50 mg once daily in a fixed-dose combination with tenofovir disoproxil fumarate lamivudine might be adequate to achieve viral suppression in adult patients with HIV and tuberculosis on a rifampicin-based tuberculosis regimen.

- A retrospective cohort study in Botswana reported virological suppression during tuberculosis therapy in 204 (95%) of 214 patients on standard dolutegravir dosing and 241 (95%) of 254 patients who received supplemental dolutegravir dosing.

- A small trial in Thailand, which randomly assigned people with HIV and tuberculosis to dolutegravir once daily or twice daily, reported virological suppression in 18 of 20 patients in both groups.

ORCHID Study Schema

- **Study design**: Sequential non-randomised pharmacokinetics study of dolutegravir (DTG) plasma exposure when given as twice or once daily DTG in the presence of rifampicin in children with Human Immune Deficiency Virus (HIV) and tuberculosis (TB) between 3-35kg in South Africa (ORCHID) (Stage 1 **using twice daily in accordance with the standard of care dosing**)

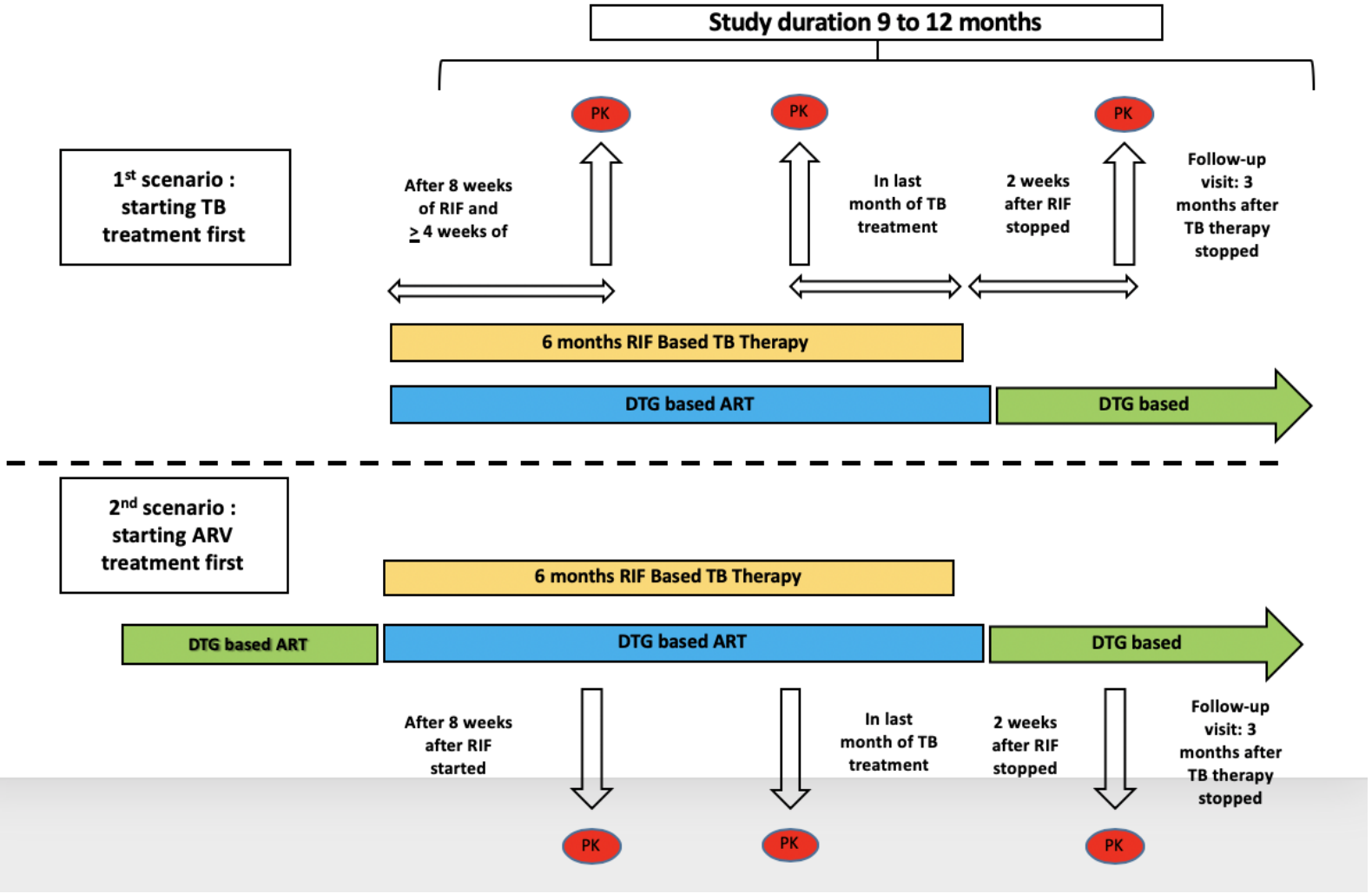
- **Study duration**: Follow-up of most children will be nine months (6 months anti-TB therapy for children already on antiretrovirals at TB therapy initiation

- **Sample size**: 12-15 (20-35kg weight band) plus 20 (*5 in each weight band*) 3-5.9 kg, 6-9.9 kg, 10-14.9 kg, 10-14.9 kg

- **Study population & key eligibility criteria**: Children >3kg and ≤35kg (> 4 weeks and < 18years) ART-naive or experienced, with plans to use DTG for HIV treatmentwith drug-sensitive TB receiving a rifampicin-based first-line TB regimen in Durban, South Africa

- **Study regimen**: DTG 50mg film-coated tablet (FCT) and 10mg dispersible tablet (DT) twice daily and RIF (weight-based dosing)

Overall study design



- Plasma samples were collected at steady-state at pre-dose, and at 1, 2, 3, 4, 6, and 12 or 24h post-dose and assayed with a validated LC-MS/MS method.
- Non-compartmental pharmacokinetic (PK) analyses were conducted using the ncappc package in R.
- The area under the concentration-time curve (AUC) was calculated using the linear-up log-down trapezoidal method. Extrapolation was done from the last measurement to 12 or 24h, using the elimination rate constant.

Pharmacokinetics and safety of dolutegravir in children receiving rifampicin tuberculosis treatment in South Africa (ORCHID): a prospective cohort study

Anushka Naidoo [1], Hylke Waalewijn [2], Kogieleum Naidoo [3], Marothi Letsoalo [4], Gabriela Cromhout [5], Leora Sewnarain [6], Nozibusiso R Mosia [6], Emmanuella C Osuala [4], Lubbe Wiesner [2], Roeland E Wasmann [2], Paolo Denti [2], Kelly E Dooley [7], Moherndran Archary [6]; ORCHID study team

- We enrolled 13 children between August 2021 to August 2023 and report the primary outcome data
- Median (IQR) age 10 (9-11) range [5-13] years; 54% males; 100% black race; 13 previously initiated on ART at baseline, 6 of these with undetectable viral load.
- The median (IQR) viral load and CD4 at baseline were 2.5 (1.6-5.0) log10-copies/mL and 108.5 (76.5-385.2) cells/µl
- **13 children had an VL >50 copies per mL at or after TB treatment completion at week 24, and 12 had a VL of >50 copies per mL at week 48.**
- There were four grade 3 adverse events - 2 events were elevated serum amylase, 1 event was raised ALT and 1 SAE (headache due to cryptococcal meningitis)

PK data for children 20-35kg

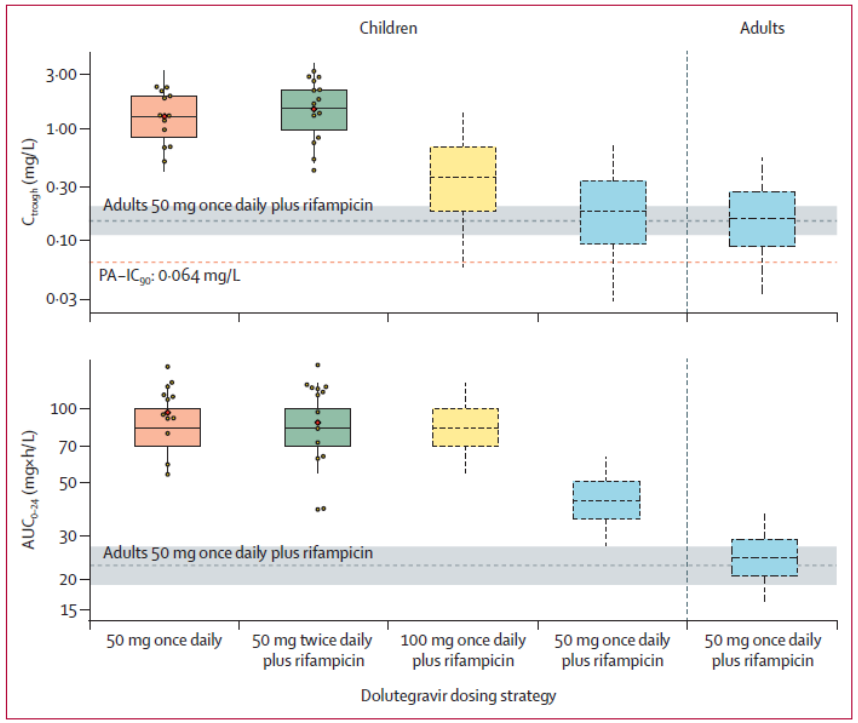


Figure 1: Simulated C_{trough} and AUC_{0-24} of different dolutegravir and rifampicin dosing strategies

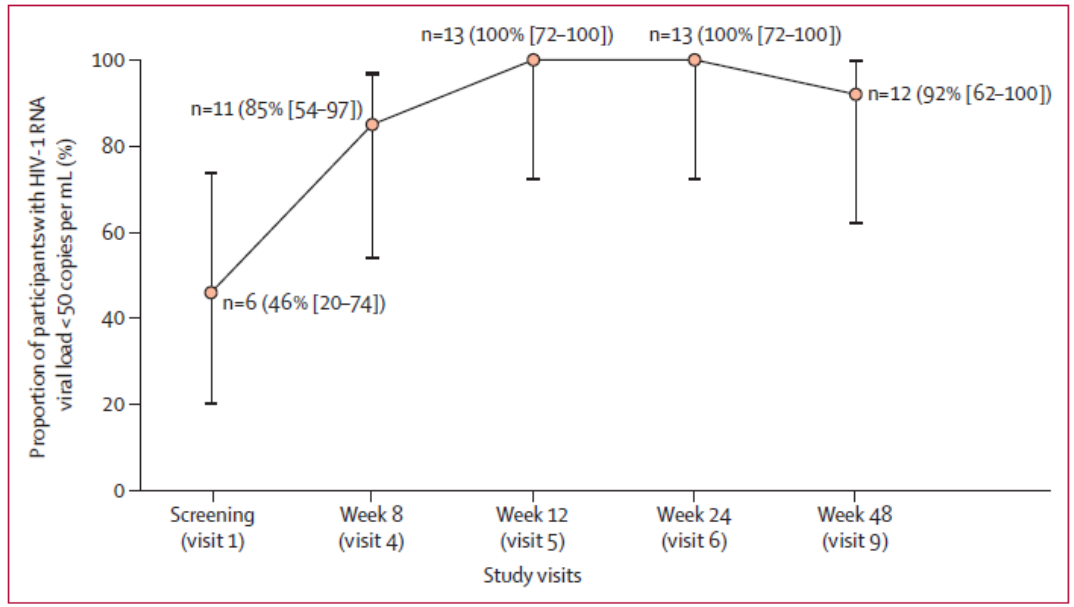


Figure 3: Viral suppression outcomes over study visit
Data in square brackets are 95% CIs.

- DTG clearance was 0·584 L/h (95% CI 0·492–0·724), with an increase in clearance of 99·1% (73·2–120) with rifampicin.

- Median Ctrough was 1·45 mg/L (coefficient of variation 68%) for participants on twice-daily DTG with rifampicin and 1·24 mg/L (70%) for participants on once-daily dolutegravir without rifampicin

Key findings

- Data from children 20-35kg receiving twice-daily dolutegravir during TB treatment suggest that this dosing is:
    - Safe, well-tolerated and achieves similar trough concentrations to daily treatment for HIV-alone.
    - Results in adequate viral load suppression and achieves target concentrations needed for virologic suppression

Anushka Naidoo[1,5], Roeland Wasmann[2], Kogieleum Naidoo[1,5], Gabriela Cromhout[3], Marothi Letsoalo[1], Leora Sewnarain[3], Nozibusiso R Mosia[3], Avanthi Moodley-Reddy[1], Lubbe Weisner[2], Paolo Denti[2], Kelly E. Dooley[4], Moherndran Archary[3] for the ORCHID Study Team

- We enrolled 21 children (3-20kg) between August 2023 and April 2025 and report preliminary data up to September 2025.
- Median (IQR) weight 9.8 (7.5-11.3); age 2.0 (1.0-3.0); 48% males; 100% black race in this cohort.
- The median (IQR) viral load and CD4 at baseline were 3.2 (2.4-4.3) log10-copies/mL and 1161.0 (652.0-1495.0) cells/µl.
- There were 14 grade 3 or higher adverse events and 9 SAEs, including one death, that were not related to study treatment.
- No treatment discontinuations due to AE's were observed. Viral load suppression (<50 copies/mL) was achieved in 73% of participants after six months of TB treatment

Results in children 3-20kg

Table 1: Dolutegravir pharmacokinetic parameters (geometric mean [%CV]) during and after TB treatment. Geometric mean ratio (GMR) for AUC0-24 and Ctau for 18 paired profiles

Parameter	DTG BID +RIF	DTG QD	GMR (90% CI)
AUC_{0-24} (h*mg/L)	74.9 (96.1%)	81.0 (55.6%)	0.924 (0.688-1.24)
C_{tau} (mg/L)	1.31 (89.6%)	0.901 (91.3%)	1.41 (0.915-2.19)

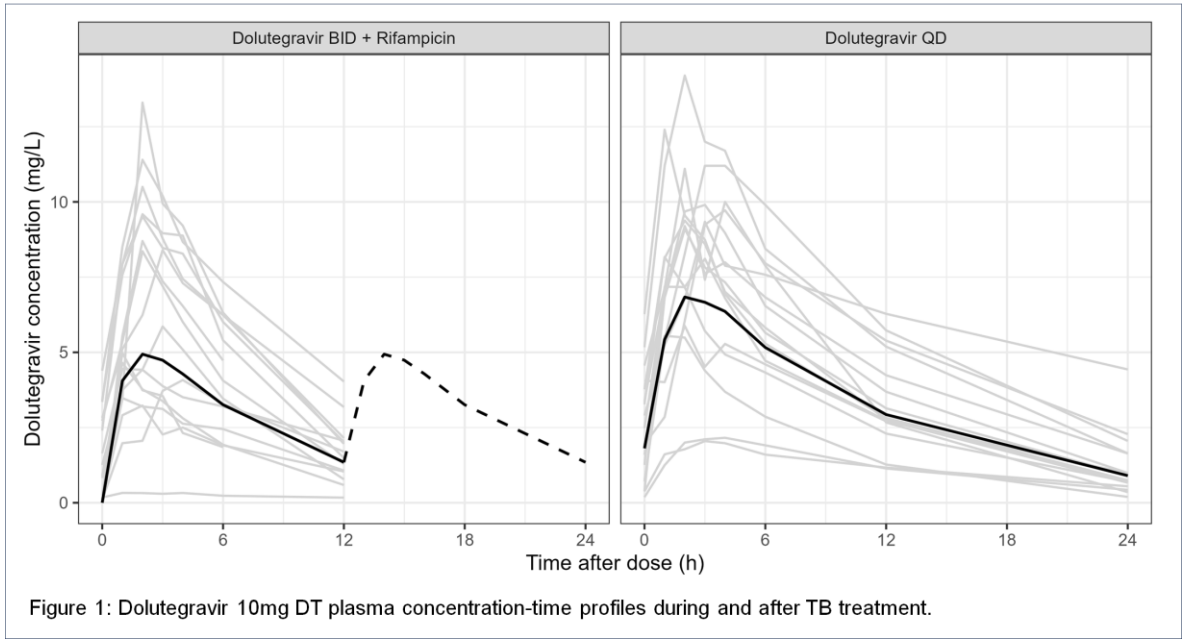


Figure 1: Dolutegravir 10mg DT plasma concentration-time profiles during and after TB treatment.

- 19 profiles on twice daily dolutegravir plus rifampicin and 18 profiles on once daily dolutegravir (total of 245 dolutegravir plasma concentration values.
- Median trough concentration (CTau) was 1.31 and 0.901 mg/L, while AUC0-24 was 74.9 and 81.0 h*mg/L for participants on BID dolutegravir with rifampicin and OD dolutegravir, respectively,

Key findings

- Preliminary data from children 3-20kg receiving twice-daily dolutegravir during TB treatment suggest this dosing strategy is safe and achieves similar PK values to daily dolutegravir without rifampicin.

- These findings support the WHO and global guideline recommendations for weight-based dolutegravir 10mg DT dosing in children 3-20kg.

ORCHID data supporting once daily DTG

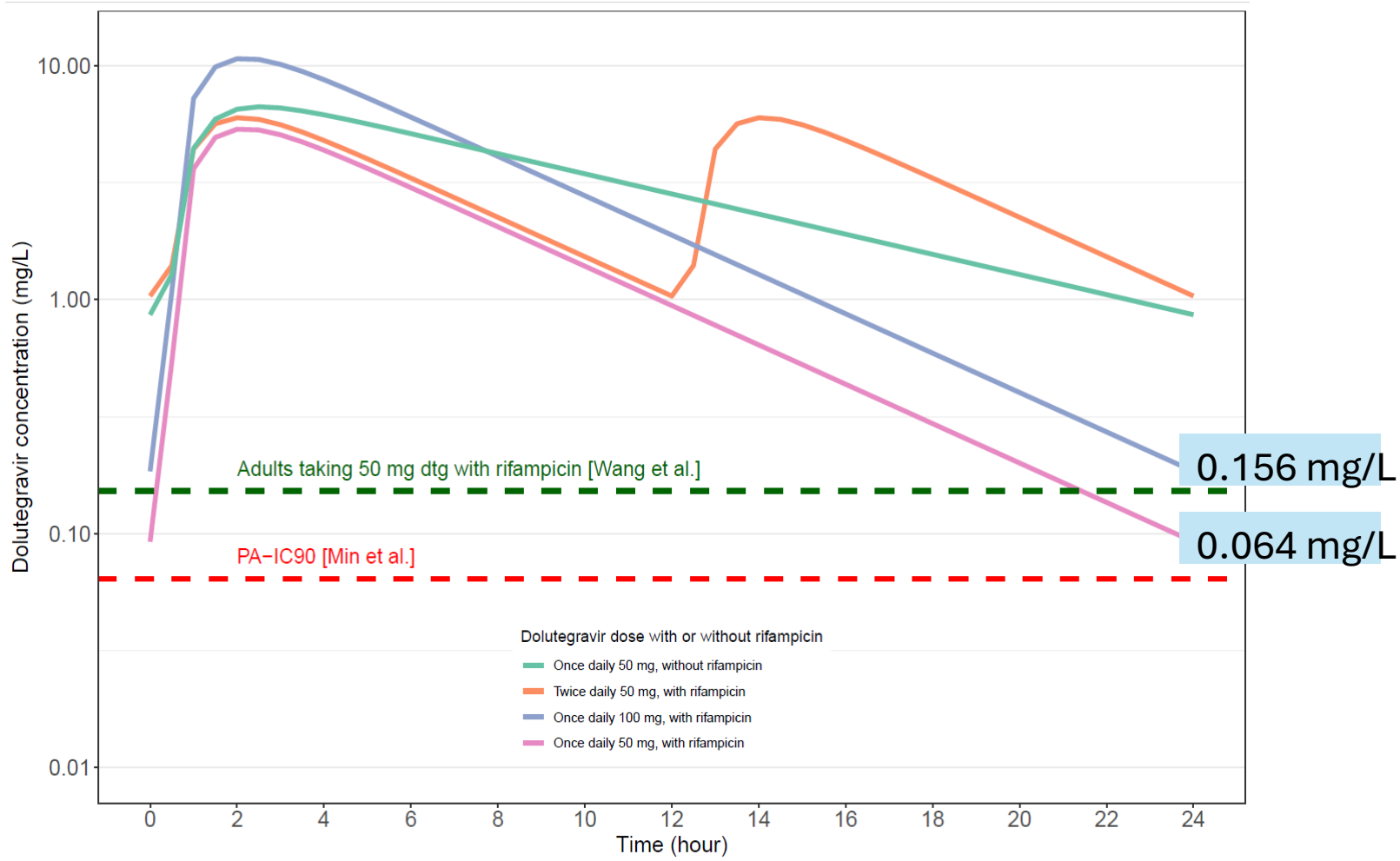
- Twice-daily DTG with rifampicin in children <35 kg achieved therapeutic concentrations and was well-tolerated with high rates of viral suppression.

- Simulations suggest that OD dolutegravir during rifampicin co-administration in children 20-35 kg should be investigated in clinical studies.

- PK model for once daily DTG dosing in children: Pharmacokinetic data from three large paediatric clinical trials [ODYSSEY (NCT02259127), CHAPAS-4 (ISRCTN22964075) and EMPIRICAL (NCT03915366)] were used to develop a paediatric population pharmacokinetic (PK) model of dolutegravir using a non-linear mixed-effects model (NONMEM).

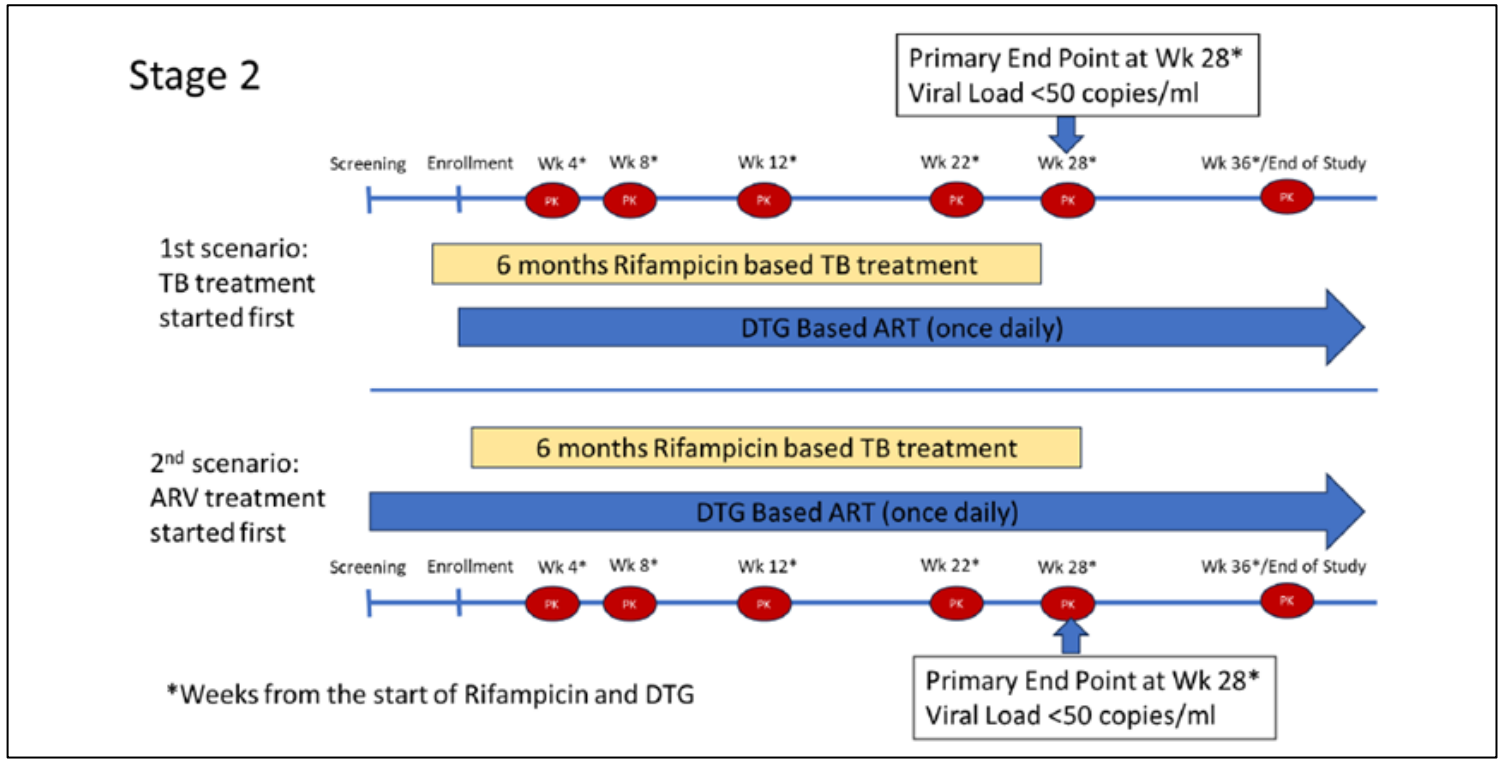
- ORCHID (NCT04746547): DTG PK data from the study were analysed using population modelling in NONMEM.

PK model for once daily DTG dosing in children



ORCHID (Stage 2)

- Stage 2 will evaluate the use of **<u>once-daily</u>** dosing of 50mg/10mg DT DTG in children (3-35kg)



Study design: An open-label, sequential, non-randomised pharmacokinetics study of DTG plasma exposure when given once-daily DTG in the presence of rifampicin-containing TB treatment in South African children and adolescents with Human Immune Deficiency Virus (HIV) and tuberculosis (TB)

Sample size : ~60

Study Duration : ~36weeks

Study population & key eligibility criteria: Children > 4 weeks and < 18years, ART-naive or experienced, with plans to use DTG for HIV treatment with drug-sensitive TB receiving a rifampicin-based first-line TB regimen in Durban, South Africa

******Watch this space-Exciting results coming soon*****

Acknowledgments

We wish to acknowledge the participants on the CAP 258 ORCHID study

The study team at CAPRISA and the Victoria Mxenge Hospital Paediatric Infectious Diseases Unit
Dr Gabriela Cromhout, Mrs Rejoice Mosia, Mrs Leora Sewnarain, Mrs Avanthi Moodley-Reddy, Ms Mpume Ndlela, Mrs Nokwazi Mthembu

Funding:
This work is supported by the National Institutes of Health and SA MRC under R01AI152142
& NIH Fogarty K43TW011437

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