ADEQUATE DOLUTEGRAVIR EXPOSURE DOSED BID WITH RIFAMPICIN IN CHILDREN 6 to <18 YEARS

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Background

- Dolutegravir (DTG)-based ART regimens are currently the preferred regimens in all children for whom DTG dose is known and DTG formulations are available, however no data are available about DTG dosing in children taking rifampicin (RIF)-containing TB treatment
- In adults, DTG BID co-administered with RIF resulted in similar DTG exposure to DTG QD without RIF*

- ODYSSEY (NCT02259127) is a randomised, non-inferiority trial evaluating efficacy and safety of 1st and 2nd line DTG-based ART vs standard of care in children living with HIV
- Children taking RIF-containing TB-treatment were included in the TB-PK substudy

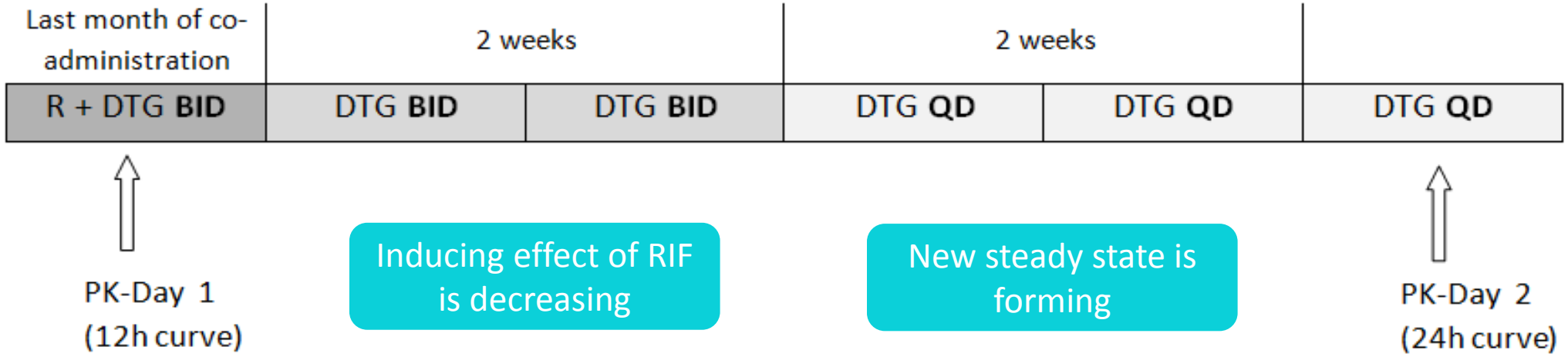
Aim

- To estimate the impact of RIF on DTG plasma concentrations in children and assess the safety of doubling DTG dose in children

* Dooley KE, et al. J Acquir Immune Defic Syndr 2013; 62:21–7

Methods & children included

Sequential intrasubject pharmacokinetic sub-study



DTG PK-sampling: Samples taken prior to DTG dose and at t= 1, 2, 3, 4, 6 and 12 or 24h (PK day 1 or 2)

31 eligible children at PK sites were included in safety analysis

17 children with PK samples analysed to date

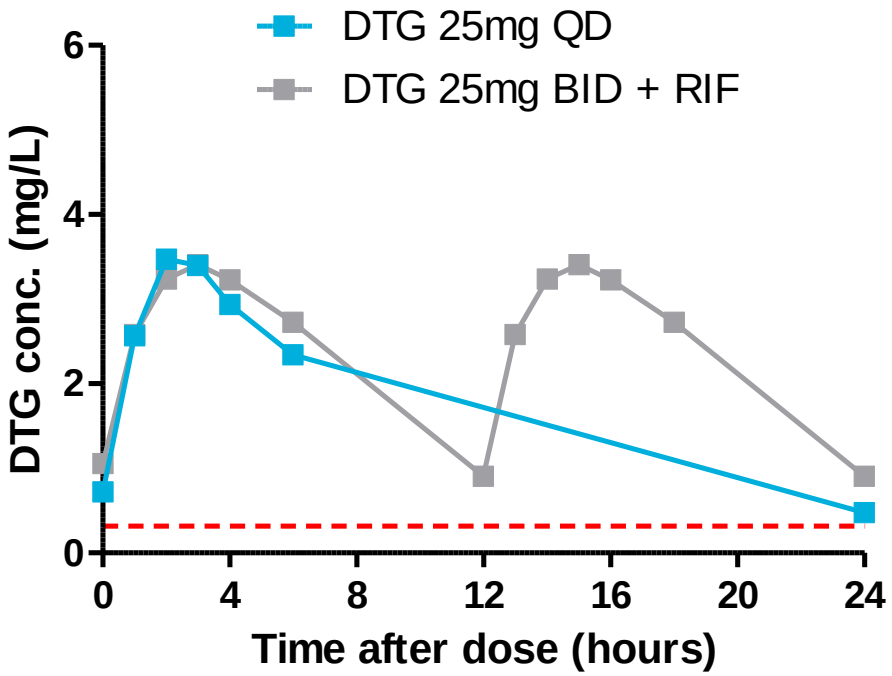
13 children with evaluable PK
- 11 with 2 samples
- 1 child, day 1 only
- 1 child, day 2 only

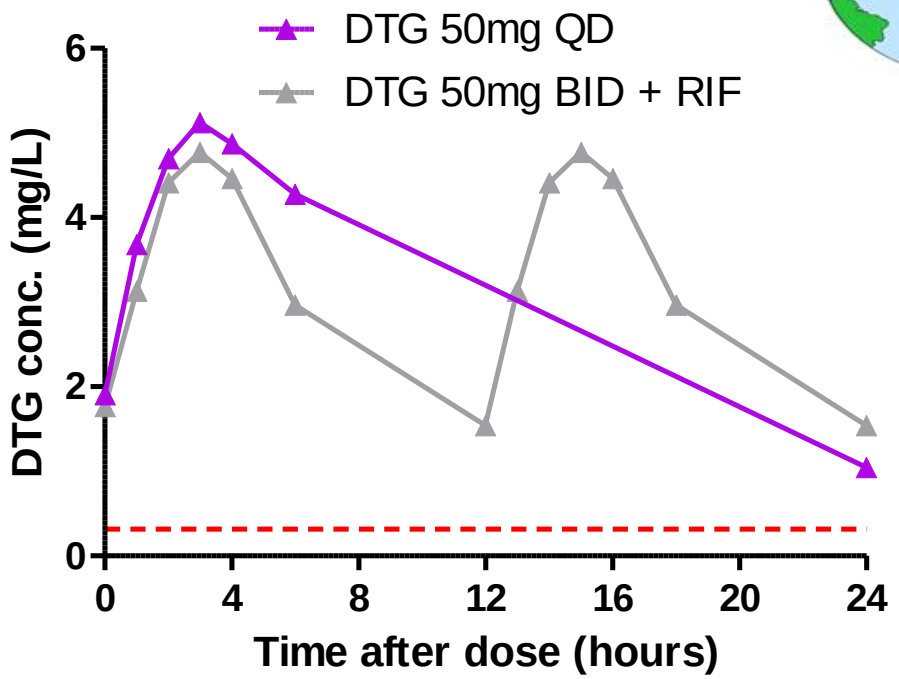
5 children on **25mg** DTG*

8 children on **50mg** DTG*

*Dose depended on weight and current Odyssey protocol

Pharmacokinetics DTG BID+RIF in children





Parameter		DTG 25mg BID + RIF (n=5)	DTG 50mg BID + RIF (n=7)	Adult reference DTG 50mg QD[1] (N=16)
C_{trough} (mg/L)	GM (CV%)	0.90 (16)	1.11 (99)	0.83 (26)
$AUC_{0\text{-}24h}$ (h*mg/L)	GM (CV%)	53.4 (21)	60.3 (63)	43.4 (20)
C_{max} (mg/L)	GM (CV%)	3.62 (24)	4.50 (47)	3.3 (16)

1. Min et al. AIDS. 2011;25(14):1737-45

Safety Data

- 31 children were followed for a median (IQR) of 30.7 (28.3, 39.6) weeks
- 13 reported safety events in 8 children
  - 9 SAEs, all hospitalizations, 1 grade 2, 4 grade 3 and 4 grade 4
    - 2 disseminated tuberculosis (1 death)
    - Hepatitis A (ART discontinuation)
    - URTI and rash
    - Acute febrile episode
    - Raised liver enzymes
    - Epilepsy, fits, convulsions
    - Deep vein thrombosis
    - Kwashiorkor with anaemia
  - 4 non-SAEs, all grade 3
    - 2 anaemia with clinical symptoms
    - 1 neutropenia
    - 1 disseminated/military TB
- All events were considered unlikely related or unrelated to DTG by investigators and Endpoint Review Committee blind to randomised allocation

Discussion and Conclusion

- Twice daily DTG dosing was safe and sufficient to overcome RIF enzyme-inducing effect in children with HIV/TB co-infection aged 6-<18 years
- These results support doubling DTG dose for children aged 6 to <18 years treated for TB with RIF-containing regimens
- Currently there are no data on doubling adult DTG dose when it is given with RIF in children weighing <25kg
- Embedding PK substudies, including PK TB-HIV drug interaction studies, in phase II/III paediatric trials accelerates obtaining key data for treating children in timely manner