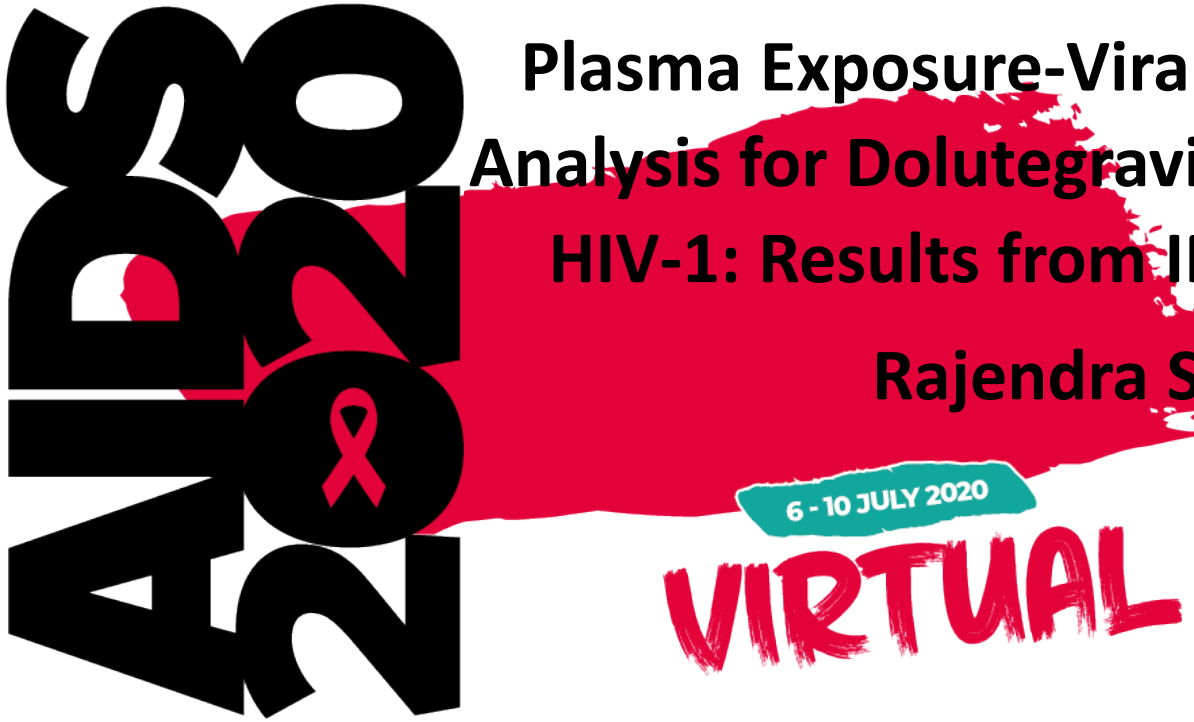


# Plasma Exposure-Viral Load Response Analysis for Dolutegravir in Children with HIV-1: Results from IMPAACT P1093

Rajendra Singh

# Plasma Exposure-Viral Load Response Analysis for Dolutegravir in Children with HIV-1: Results from IMPAACT P1093

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# Background and Objective

- Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of Dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

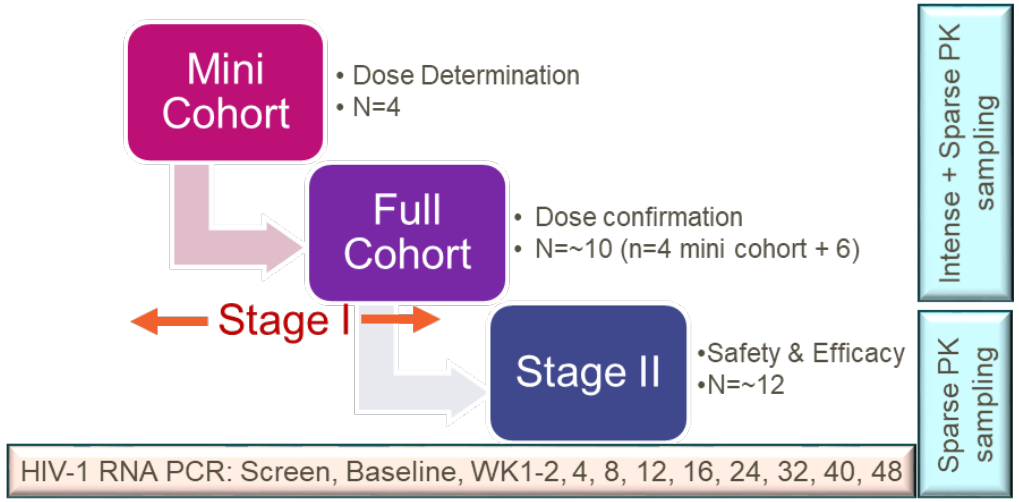
- Regulatory (FDA, EMA) guidance suggests a drug's efficacy in children can be extrapolated from adult trial data, if similar PK exposures are obtained.

- P1093 participants who experienced virologic failure generally reported problems with medication adherence, but it remained possible that low drug exposures were playing a role.

- OBJECTIVE: To determine if drug exposures in P1093 were predictive of virologic outcomes

# IMPAACT Study P1093 Design

- Study Design




| | |
|---|---|
| Cohort I: | Adolescents ≥12 to <18 years of age (Tablet formulation) |
| Cohort IIA: | Children ≥6 to <12 years of age (Tablet formulation) |
| Cohort IIB: | Children ≥6 to <12 years of age (Granules) |
| Cohort III: | Children ≥2 to <6 years of age (Granules/Dispersible Tablet) |
| Cohort IV: | Children ≥6 months to <2 years (Granules/Dispersible Tablet) |
| Cohort V: | Infants ≥4 weeks to <6 months (Dispersible Tablet) |

# Viral Load Response Modeling

Method and Results:

- Enrollment has closed in this study with N=181 participants. At the time of the analysis a total of 143, 135 and 112 VL response observations were available at Weeks 4, 24 and 48, respectively.
- The probability of virologic response (VR, HIV-1 RNA <50 or <400 copies/mL at Weeks 4, 24 and 48) was modelled as a function of DTG exposure (C24, Cavg or AUC0-24) using Logistic regression analyses in NONMEM (version 7.4.3).
- Covariates tested were baseline viral load (BVL), CD4+ count, CDC HIV infection stage and baseline VL ≥100,000 copies/mL.
- The covariate VL ≥100,000 copies/mL at enrolment was a significant predictor of virologic response HIV-1 RNA <50 copies/mL at Weeks 4 and 24 (p value < 0.01). VL ≥100,000 copies/mL at enrolment was NOT predictive of virologic response HIV-1 RNA <400 copies/mL at either Weeks 24 or 48.

# Viral Load Response Modeling

Working together in HIV

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Results:

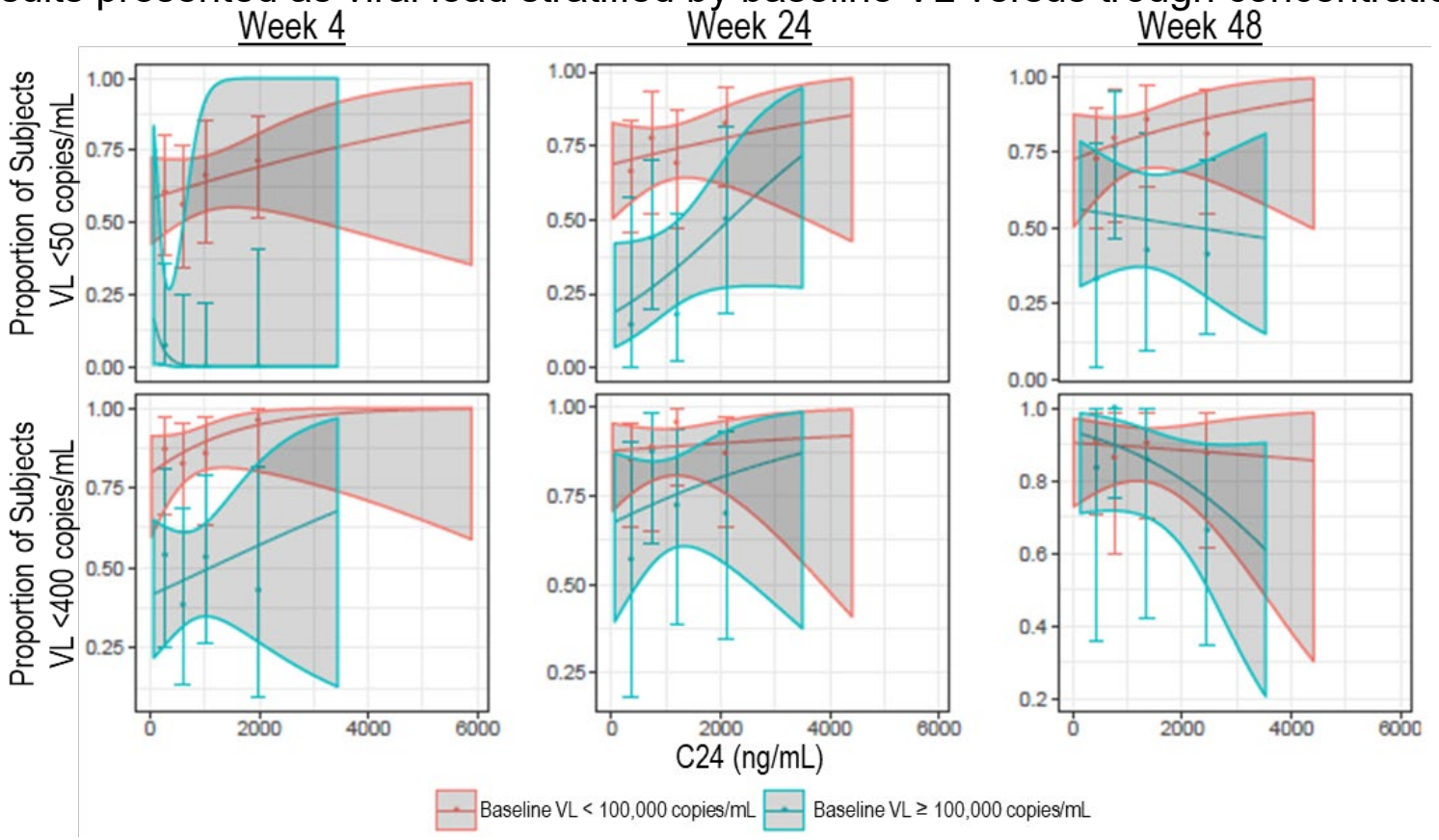
Overall model predicted proportion of subjects achieving HIV-1 RNA 400 copies/mL or <50 copies/mL at weeks 4, 24 and 48.

| Week | Model Predicted Response VL<50 Copies/mL (%) | Model Predicted Response VL<400 Copies/mL (%) |
|---|---|---|
| Response at Week 4 | 43 | 75 |
| Response at Week 24 | 61 | 84 |
| Response at Week 48 | 71 | 88 |

# Viral Load Response Modeling

VL response (<400 and <50 copies/mL) versus **Trough (C24) concentrations**

Results presented as viral load stratified by baseline VL versus trough concentrations.

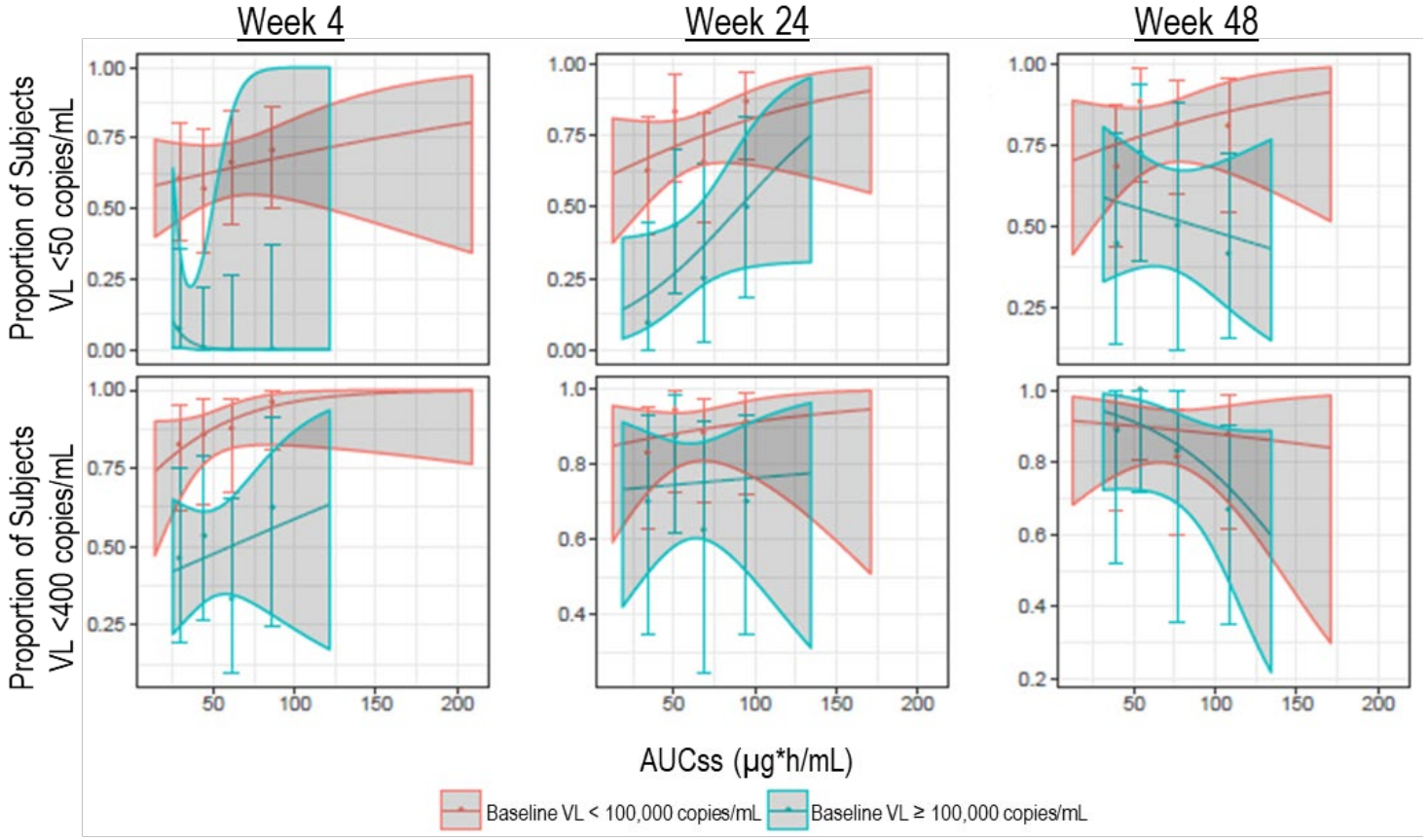



No apparent relationship between trough (C24) concentrations and viral load response at doses studied suggesting studied doses are at plateau (maximum) of dose response curve.

# Viral Load Response Modeling

VL response (<400 and <50 copies/mL) versus **Steady state $AUC_{0-24}$**

Results presented as viral load stratified by baseline VL versus AUC




No apparent relationship between steady state AUC0-24 concentrations and viral load response at doses studied suggesting studied doses are at plateau (maximum) of dose response curve.

# Conclusion

- In IMPAACT P1093, a wide range of exposures ($C_{24}$, $AUC_{0-24}$ and $C_{avg}$) were observed at tested doses.
- DTG exposure metrics at doses studied were not correlated with VL response, suggesting that the doses tested are in a range where maximum drug effect is experienced.
- Baseline VL was a significant predictor of response suggesting participants with >100,000 copies/mL at baseline had lower probability to achieve <50 copies/mL at week 4 and 24 as compared to those with <100,000 copies/mL.