

Meta-analysis of Pharmacokinetic- Pharmacodynamic Relationship of Integrase Inhibitors

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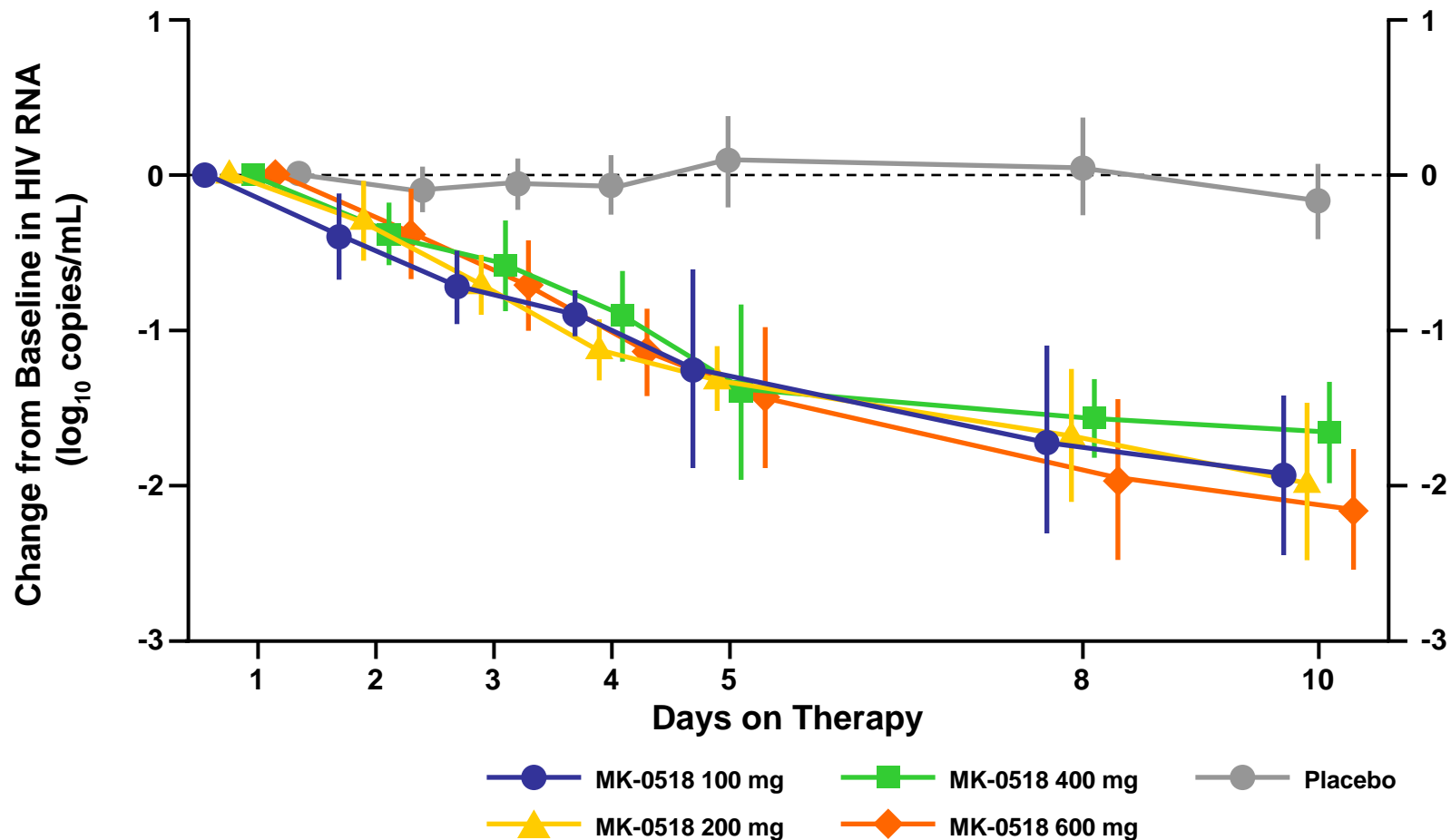
Why Demonstrating PK/PD Relationship is Important

- **Confidence in Dosing**
 - What dose/exposure works and not works
- **Define clinically significant threshold: e.g. food effect, drug interaction,**
- **Dose adjustment in special populations (peds, hepatic impairment, renal impairments, etc) or subgroup (age, gender, race)**
- **Evaluate the risk/benefit ratio**

The objective of this analysis is to evaluate the similarity or difference in PK/PD relationship of integrase inhibitors as a class in short-term monotherapy (Phase2a)



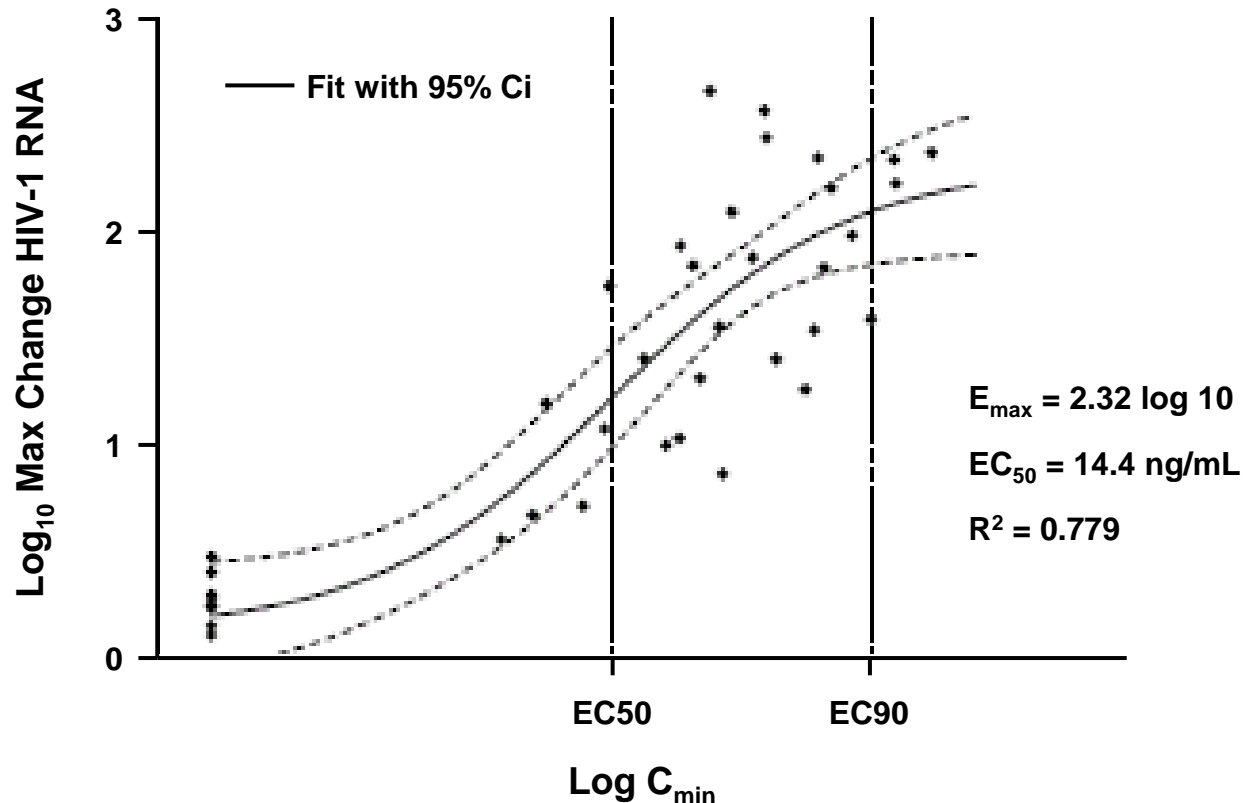
Raltegravir (RAL): No Dose/Exposure - Response Relationship



Ref: Markowitz, JAIDS 2006, 43 (5):509-515.

Elvitegrair (ELV): Cmin Predicts Activity

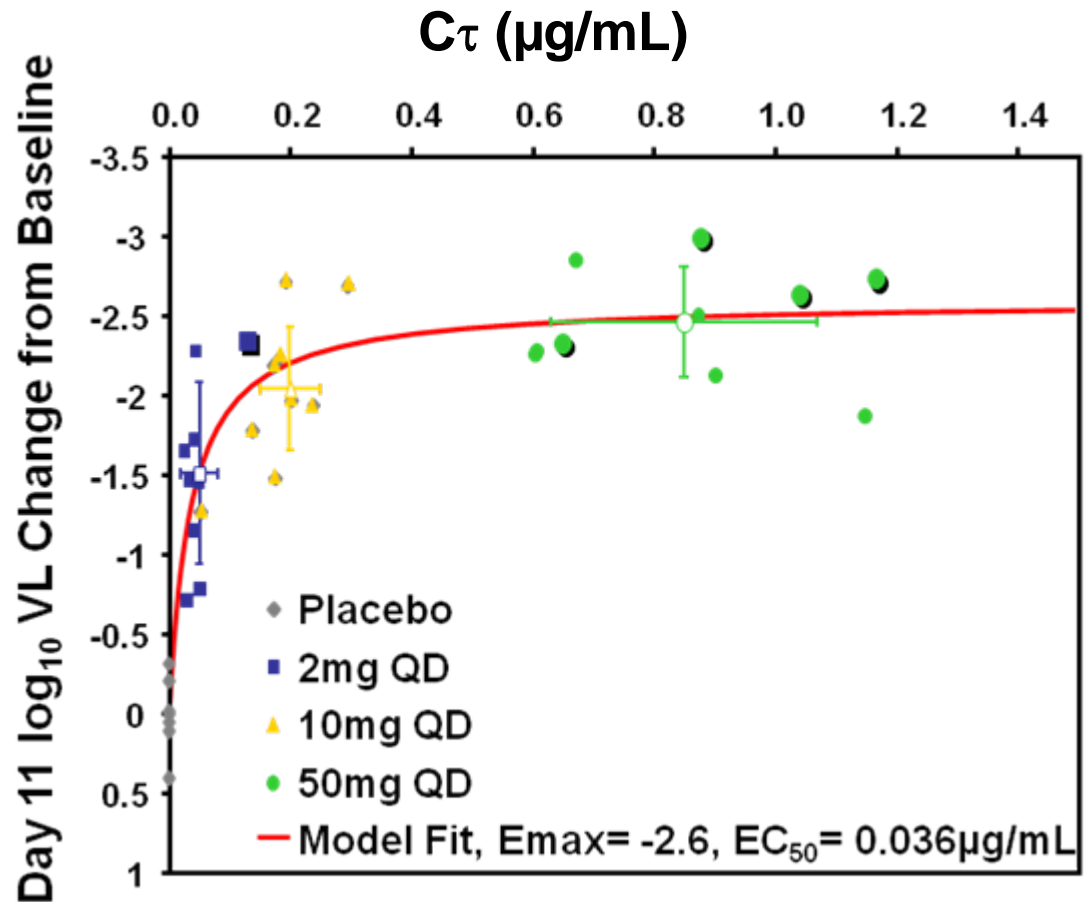
Emax Monotherapy Dose-Response Model for GS-9137



Ref: DeJesus 2006, JAIDS, 43(1)1-5.

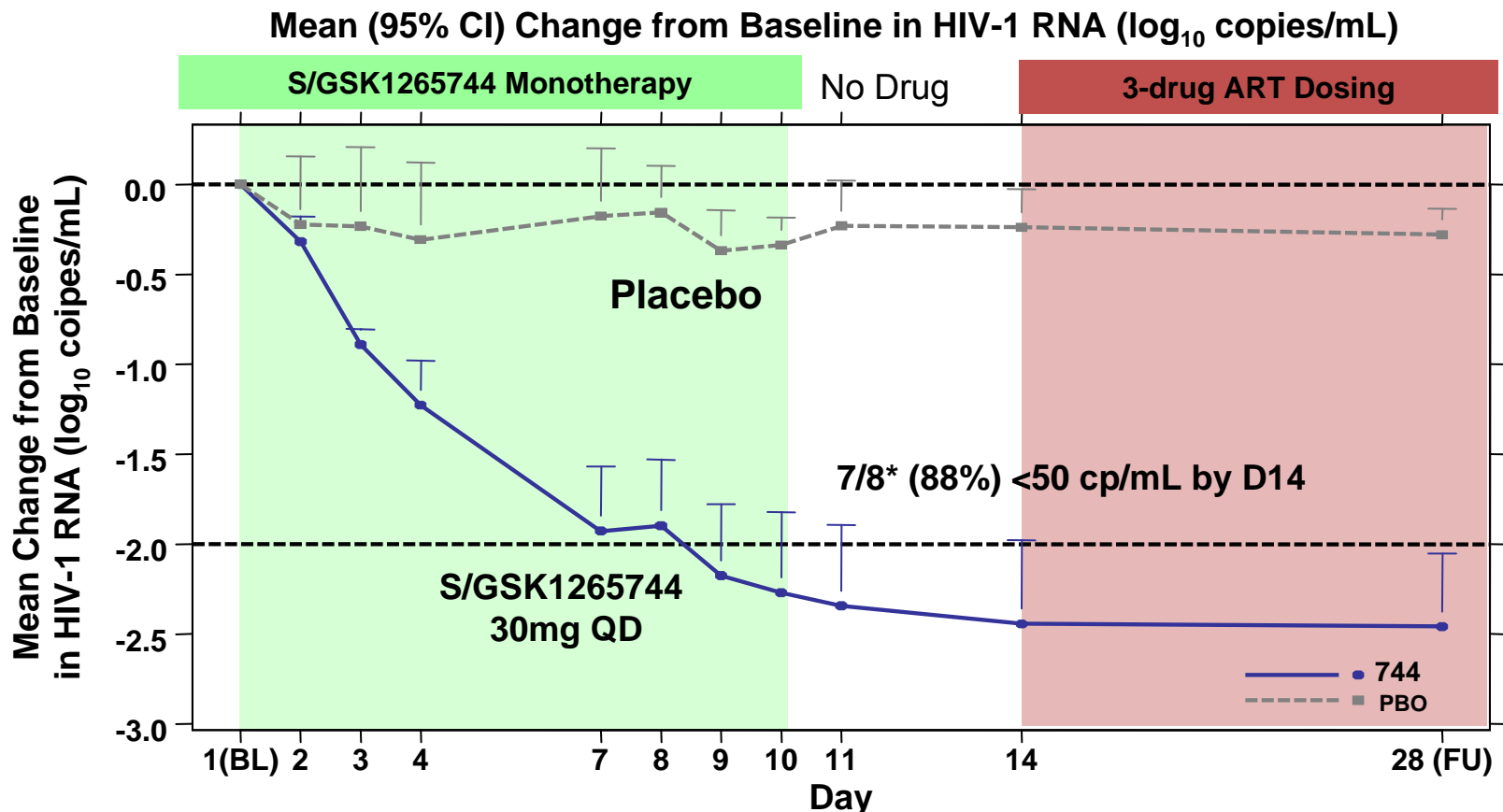
*Five treatments: 800mg QD, 200mg BID, 400mg BID, 800mg BID, and 50mg/r QD.

S/GSK1349572 (572): C_{τ} Predicts Activity



Ref: Song, IAS 2009, Cape Town. Abstract WEPEB250.

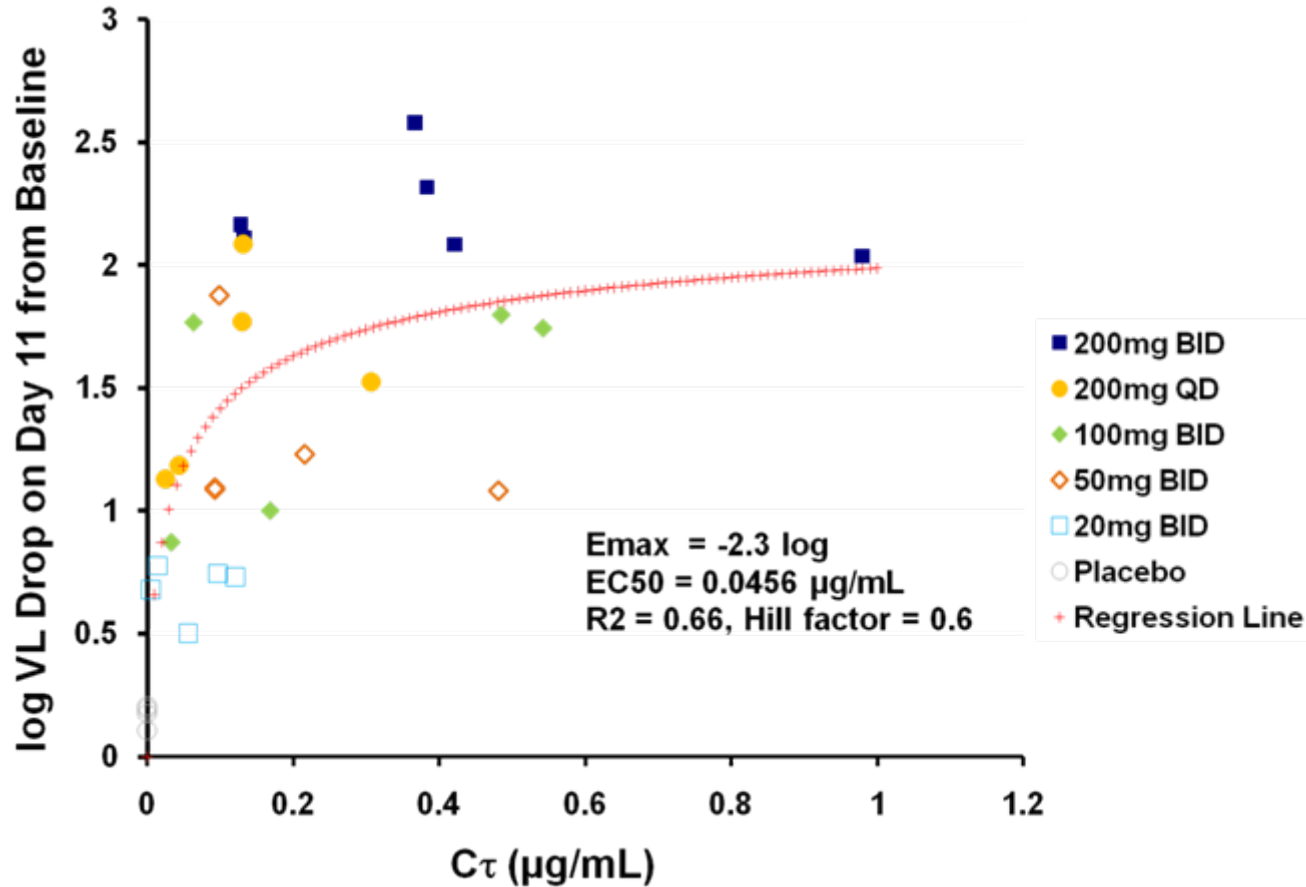
S/GSK1265744 (744): Antiviral Activity (30mg QD)



	Median HIV-1 RNA Decline Baseline to Day 11	Range	CD4
S/GSK1265744	-2.6 \log_{10} cp/mL	(-3.0, -1.0)	+15 (-100, +100)
Placebo	-0.27 \log_{10} cp/mL	(-0.4, 0.0)	-90 (-190, -20)

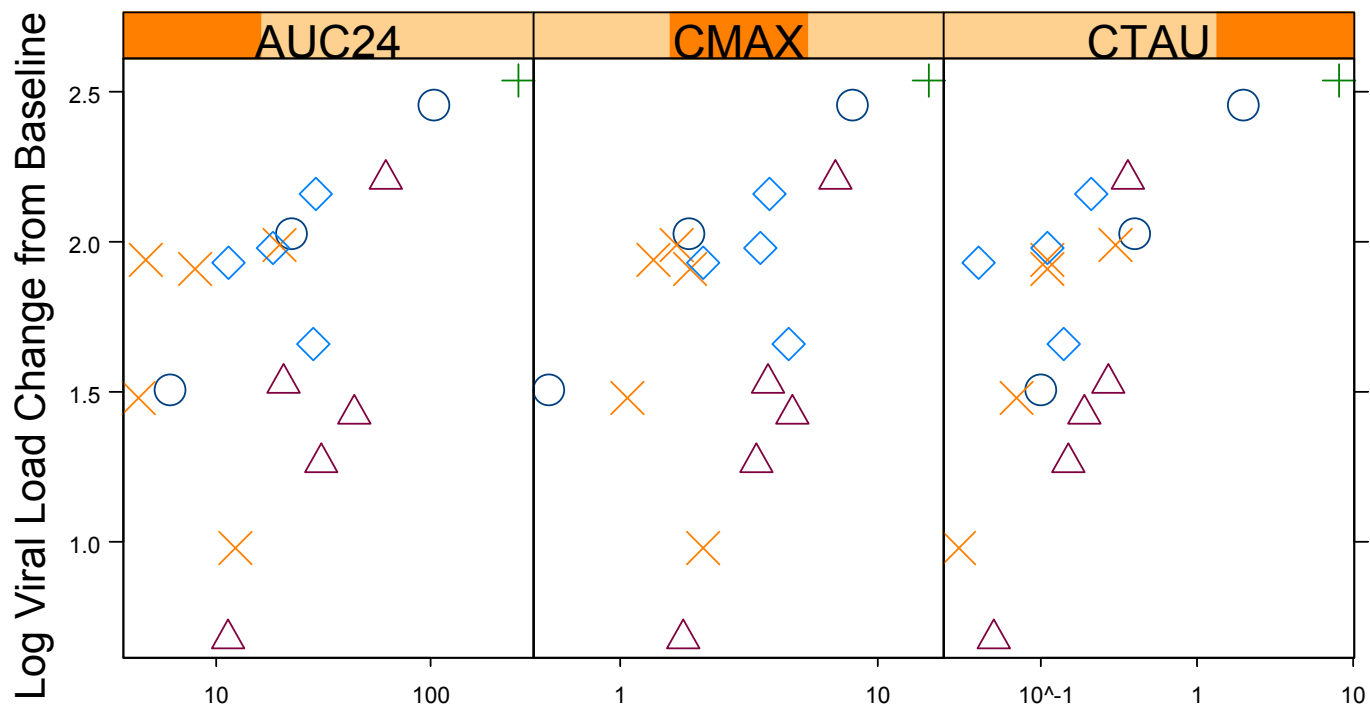
*1 subject with screening VL of 8410 cp/mL had HIV-1 RNA of 474 cp/mL at Day 1.
 Min, et al. 49th ICAAC, 12–15 September 2009, San Francisco, CA, USA. Abstract #H1228.

S/GSK364735 (735): C_{τ} Predicts Activity



Ref: Golden etc. 47th ICAAC, Sept.17-20 2007, Abstract H-1047; Unpublished Analysis.

What if We Pool All INI PK/PD Data Together?



○ 572 + 744 ◇ RAL
 △ 735 × ELV

*Data presented are treatment means.

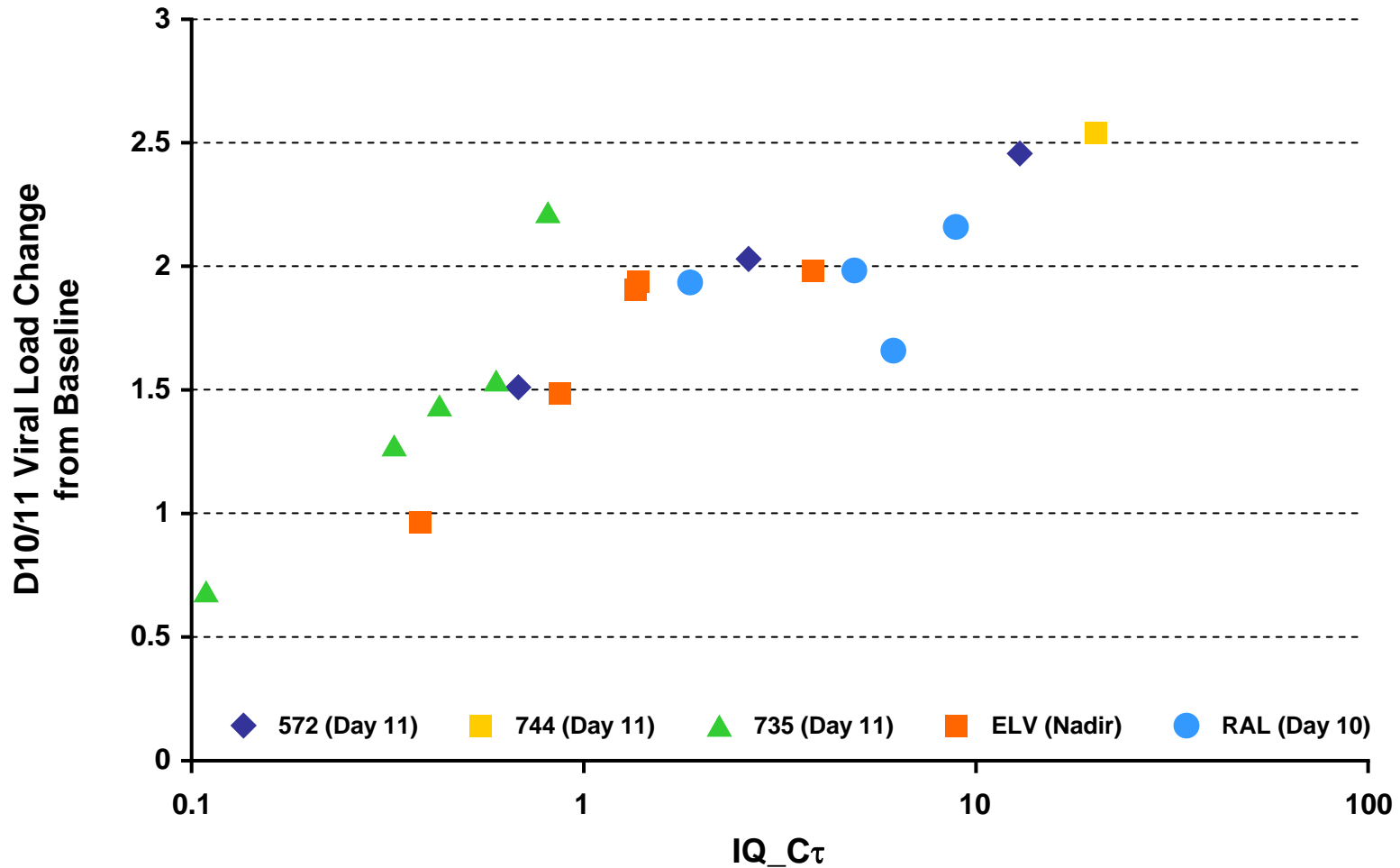
Meta-Analysis

- Inhibitory Quotient (IQ): = C_{τ} / PA-IC90
- PA-IC90 (protein-adjusted IC90), determined for all drugs using the same in vitro assay and viral strand

Drug	RAL	ELV	572	744	735
PA-IC90 (nM)	23	78	152	400	441

- Mean steady state PK (AUC, C_{max}, and C_τ) and mean Day10/11 viral load change from baseline by treatment/dose: obtained from publications
- Models examined: linear and various E_{max}
 - PK: IQ_AUC = AUC_{24/24}*PA-IC90,
IQ_C_{max} = C_{max}/PA-IC90,
IQ_C_τ = C_τ /PA-IC90
 - PD: Day11 VL change from baseline
- Model comparison was based on Akaike Information Criteria (AIC)

Using IQ, INIs Show a consistent PK/PD Relationship



An In-depth Look at Raltegravir PK/PD

- **Merck's position: antiviral activity reached plateau at dose range of 100-600mg BID**
- **Likely true for long-term combination therapy with potent background ART**
- **Not true for short-term data**
 - **Meta-analysis: RAL achieved VL drop of ~2log, lower than 572 (50mgQD) and 744 (30mg QD) due to lower IQ achieved**
 - **% subjects achieved <50c/mL on Day10/11 in Phase2a: 572 and 744 achieved high %<50c/mL than RAL**

Drug	RAL	572	744	735
%<50c/mL	100mgBID:14% (1/7) 200mgBID: 29%(2/7) 400mgBID:17%(1/6) 600mgBID:13%(1/8)	2mgQD: 11% (1/9) 10mgQD:0% (0/9) 50mgQD: 40(4/10)	30mgQD: 63%(5/8)	20mgBID:0% (0/5) 50mgBID:0% (0/5) 200mgQD: 0% (0/5) 100mgBID: 0% (0/5) 200mgBID:33%(2/6)

Model Evaluation (AIC): C_{τ} is the Best Predictor of Antiviral Activity

Model	IQ_AUC	IQ_Cmax	IQ_C $_{\tau}$	
$PD = \frac{E_{max} * PK}{EPK50 + PK}$	18.1	21.5	0.3	Best model
$PD = \frac{E_{max} * PK^{\gamma}}{EPK50^{\gamma} + PK^{\gamma}}$	20.0	23.3	2.2	
$PD = \frac{E_{max} * \log_{10}(PK)}{EPK50 + \log_{10}(PK)}$	23.9	22.0	22.9	
$PD = \frac{E_{max} * (\log_{10}(PK))^{\gamma}}{EPK50^{\gamma} + (\log_{10}(PK))^{\gamma}}$	17.9	22.0	0.1	
$PD = a + b * \log_{10}(PK)$	25.8	36.9	52.3	

- Parameter estimates of best model: mean [95%CI]
 $E_{max} = 2.25 [2.06, 2.44]$, $EC50 = 0.28 [0.16, 0.40]$

Summary

- **The antiviral activity of INI class appears to be primarily driven by C_{τ}**
- **572 and 744 demonstrated the largest declines in viral load compared to other INIs at the highest doses studied in short-term monotherapy and the superior potency is attributable to the high IQs achieved**
- **The PK/PD relationship of INIs identified in this meta-analysis can be utilized in Phase2a study to optimize dose selection**