Population PK and Viral Dynamic Modeling of S/GSK1349572 in Patients with HIV Infection

J. Zhang[1], T.E. Kim[2], J. Kim[1], I. Song[1]

[1]GlaxoSmithKline, RTP, NC, USA

[2]University of North Carolina, School of Pharmacy, Chapel Hill, NC, USA

SHIONOGI

ViiV Healthcare

11th International Workshop on Clinical Pharmacology of HIV Therapy
7-9 April 2010, Sorrento Italy

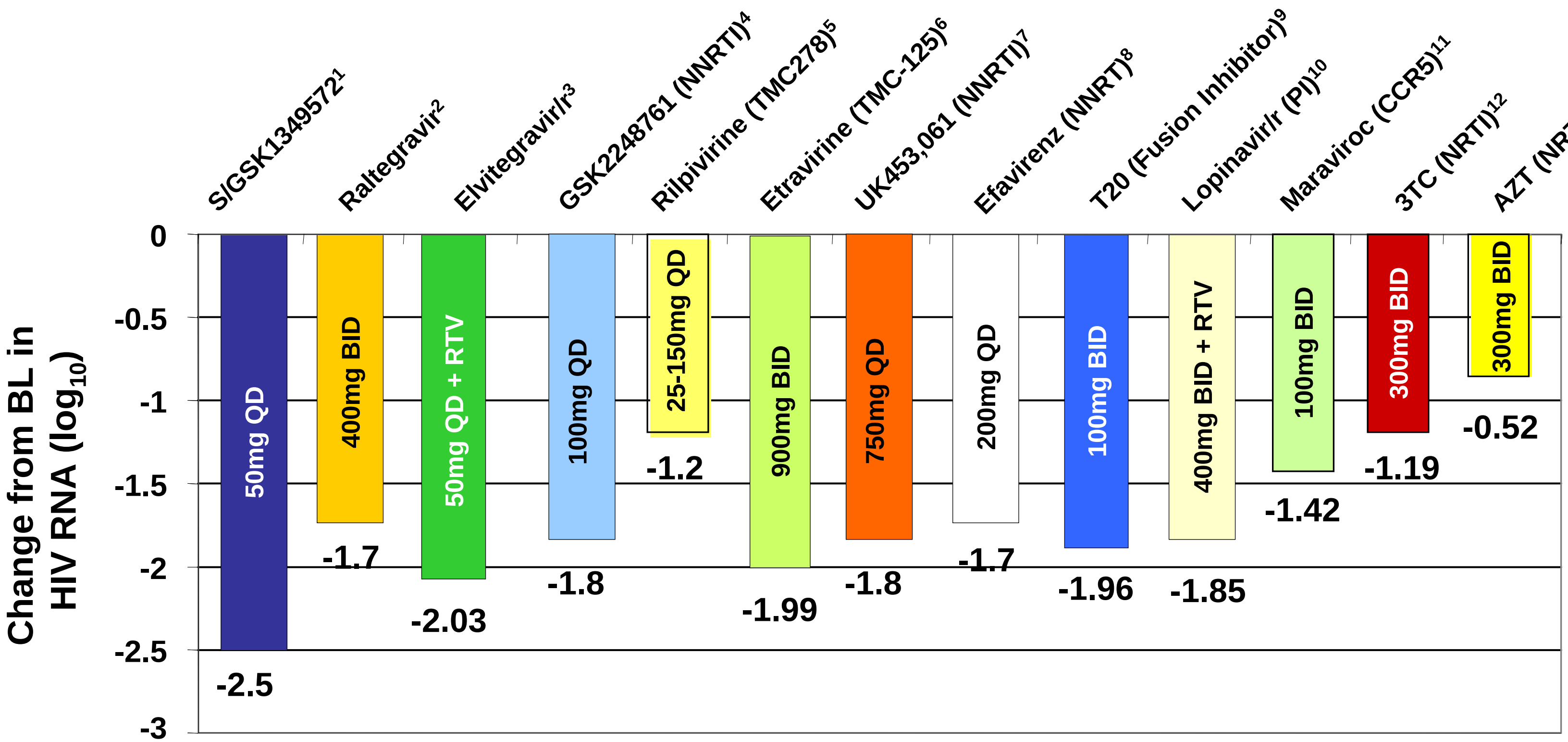
Objectives

Develop a population PK-viral dynamic model to characterize the relationship between plasma 572 concentrations and HIV viral decline in HIV-infected patients

↓

- Explore the underlying mechanism
- Optimize dose selection for future studies
- Address clinical relevant questions
  e.g., Resistance, DDI, ...

572 exhibited potent antiviral activity following 10-day monotherapy in INI-naïve HIV patients



** *Approved dose for etravirine is 200mg BID*

1. Lalezari J. 5th *IAS 2009*, *Cape Town*, abstract 2120.
2. DeJesus E. *J Acquir Immune Defic Syndr* 2006 ; 43:1-5.
3. Markowitz et al. *JAIDS* Volume 43(5) 15 December 2006 pp 509-515.
4. Zala et al, IAS (Mexico City) 2008 abstract THAB0402.
5. Goebel et al. AIDS 2006, 20:1721–1726.
6. Sankatsing et al. AIDS 2003, 17:2623–2627.
7. Fätkenheuer G, et al. IAS 2007. Abstract WESS202.
8. Adkins et al. Drugs 1998, 56(6): 1055-1064
9. Kilby JM. AIDS Res Hum Retroviruses 2002; 18:685-694.
10. Murphy RL. AIDS 2001;15:F1-F9.
11. Fätkenheuer G et al. *Nat Med* 2005 Nov; 11:1170-1172.
12. Eron JJ, *N Engl J Med* 1995, 333:1662-1669.

Proposed Hypotheses for Potent Antiviral Activity of 572

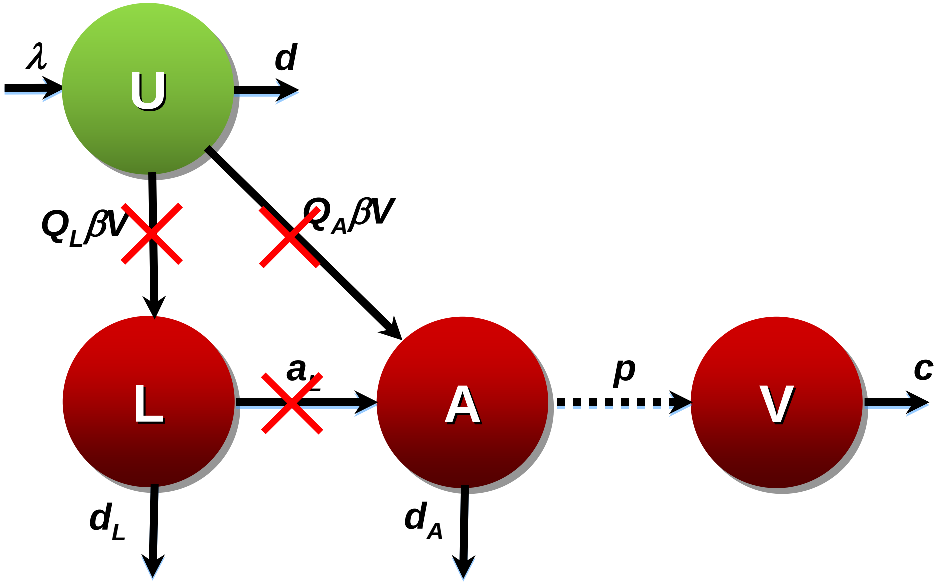
U: Uninfected CD4+ cells

A: Actively infected cells

L: Latently infected cells

V: Infectious virus

Funk, et al., JAIDS 2001; 26:397-404.
*Murray, et al. AIDS 2007, 21:2315-2321.



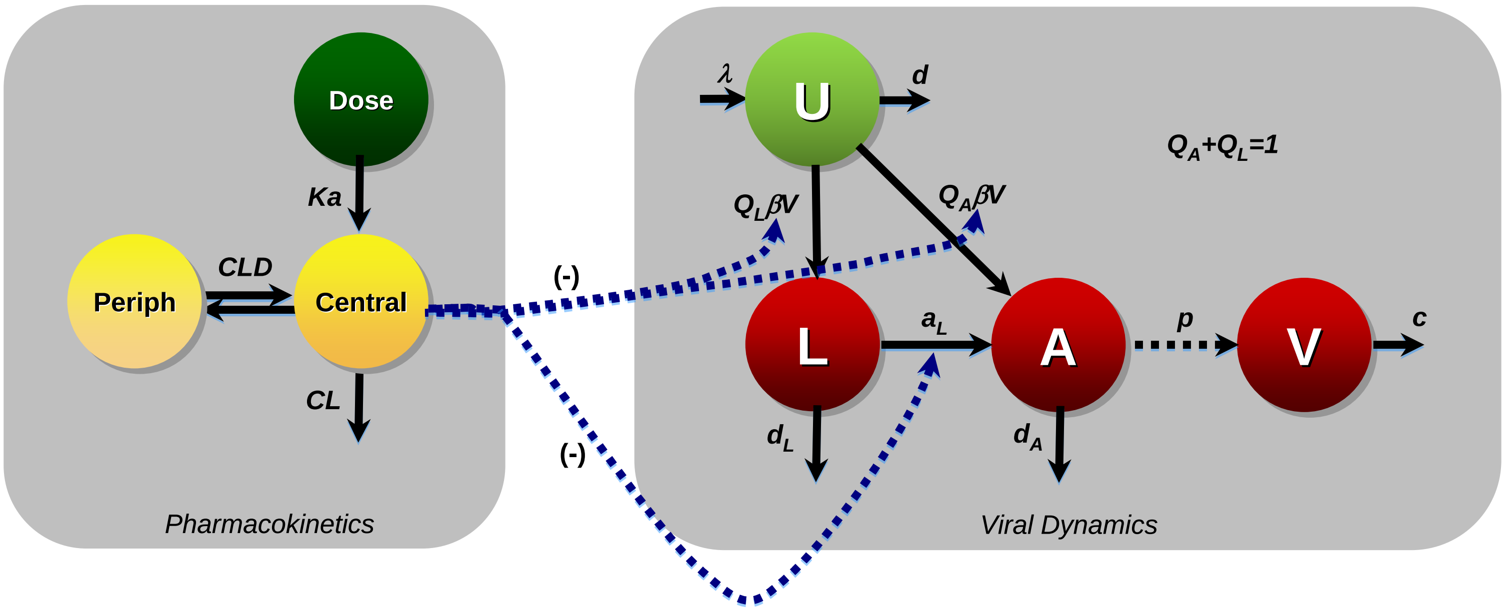
Hypothesis 1: **INI acts like traditional anti-HIV drugs with increased potency in suppressing the viral infectivity**

Hypothesis 2*: **In addition to suppression of viral infectivity, INI also blocks viral DNA integration in latently infected cells**

Phase 2a Study Design of 572

- Randomized, parallel, double-blind, dose ranging, placebo-controlled;
- INI naïve HIV infected adults;
- Daily dose of 2mg, 10mg, 50mg or placebo over 10 days;
- Active treatment (n=8) vs matching placebo (n=2) in each dose cohort;
- Rich PK samples on Days 1 and 10 with additional pre-dose samples in between;
- Daily viral load up to Day 11 plus additional viral load on Days 14 & 20 were obtained

PK/PD Model Structure



$$\text{Model 1:} \quad I_\beta(C) = 1 - \frac{C}{C + IC50}$$

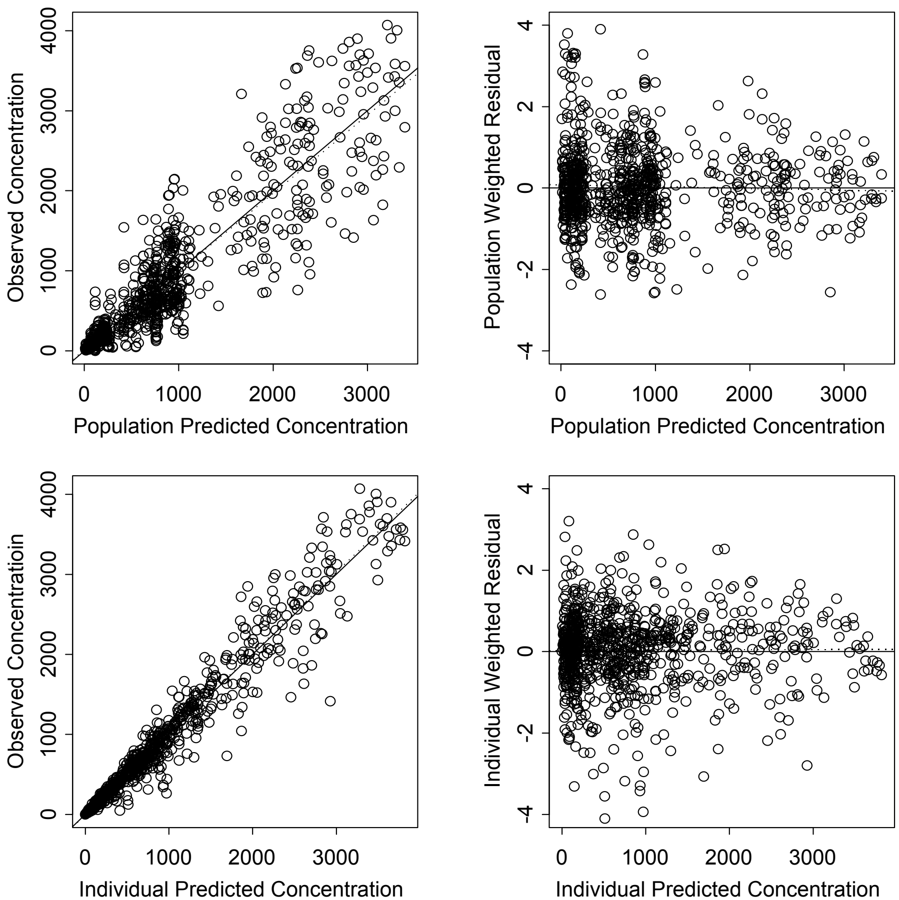
$$\text{Model 2:} \quad I_\beta(C) = 1 - \frac{C}{C + IC50} \quad \& \quad I_{a_L}(C) = 1 - \alpha$$

Population PK Results

Parameter	Estimate	%CV
ka (1/hr)	1.47	60.8
CL/F (L/hr)	1.19	33.2
Vc/F (L)	17.9	34.6
CLD/F (L/hr)	0.26	-
Vp/F (L)	1.73	-
Alag (hr)	0.18	60.8
Age~CL/F	0.34	-
σ^2	0.034	-

$$CL/F \text{ increases with age by } \left(\frac{age}{38}\right)^{0.34}$$

Goodness of Fit



Viral Dynamic Model Results

Input Variable	Symbol	Units	Typical Value
Death (clearance) rate of uninfected CD4+ cells	d	1/day	0.006[a]
Death (clearance) rate of actively infected CD4+ cells	d_A	1/day	0.72[a]
Death (clearance) rate of latently infected CD4+ cells	d_L	1/day	0.03[a]
Reactivation rate of latently infected CD4+ cells	a_L	1/day	0.036[b]
Fraction of infected CD4+ cells that become actively infected	Q_A	––	0.97[a]
Fraction of infected CD4+ cells that become latently infected	Q_L	––	0.029[a]
p=viral production rate from actively infected CD4+ cells; c=viral death (clearance) rate	p/c	copies/ cell	35.4[a]

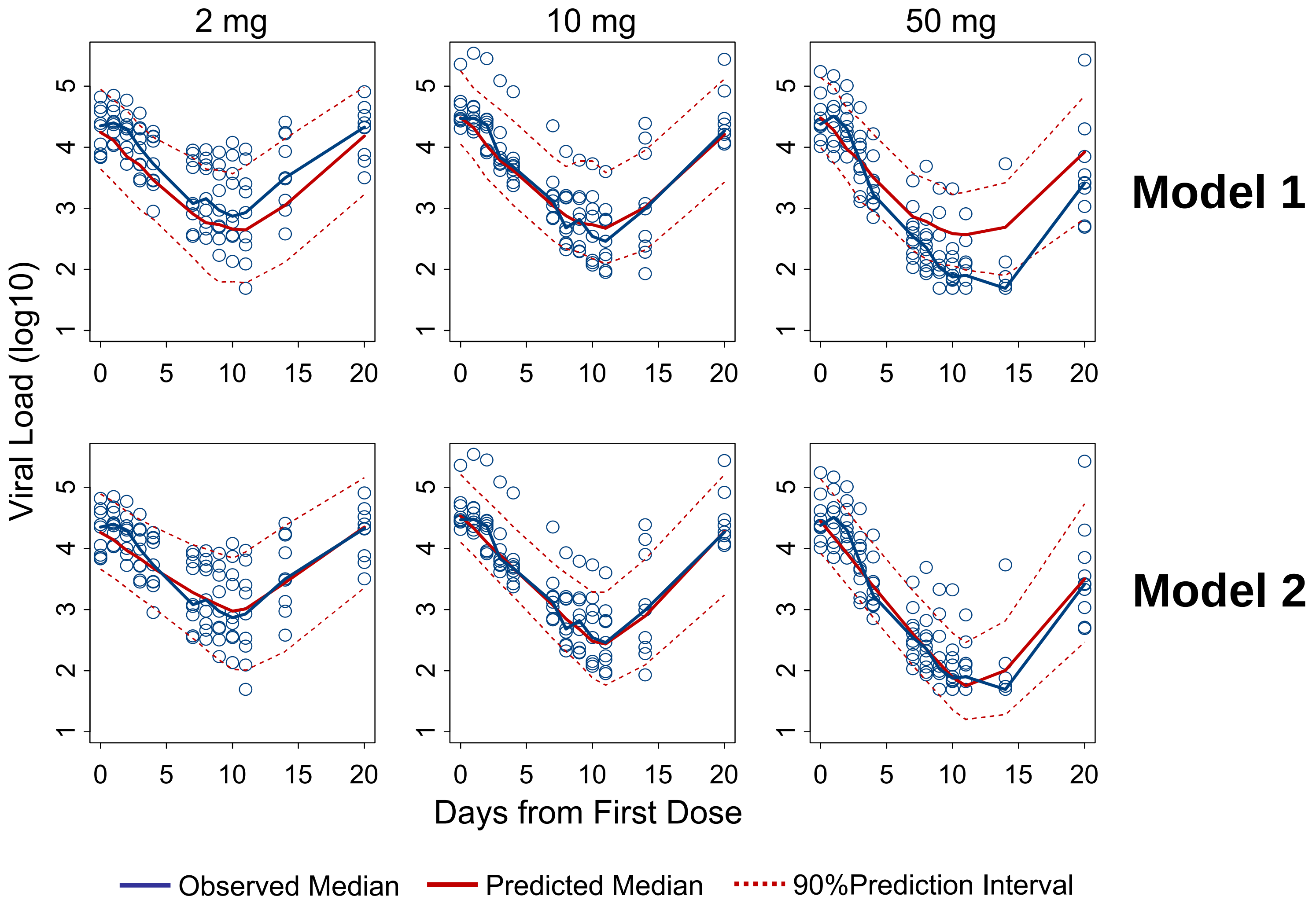
[a]Funk, et al., JAIDS 2001; 26:397-404.
[b]Phillips, Science 1996; 271:497-499.

$$\text{Model 1:} \quad I_\beta(C) = 1 - \frac{C}{C + IC50}$$

$$\text{Model 2:} \quad I_\beta(C) = 1 - \frac{C}{C + IC50} \quad \& \quad I_{a_L}(C) = 1 - \alpha$$

Parameter	Estimate (%CV)	
	Model 1	**Model 2**
R_0	9.4 (41)	10.3 (39)
IC50 (ng/mL)	7.56 (231)	72.7 (70)
α	-	0.96
d_A *(1/day)*	0.63	0.65
σ^2	0.076	0.048
Parameter	**Derived (%CV)**	
	Model 1	**Model 2**
β *(1/(copies/µL)/day)*	0.0020 (85)	0.0018 (86)
λ *(cells/µL/day)*	0.66 (78)	0.64 (77)
Objective Function	-501.6	-667.4

Model Evaluation and Comparison

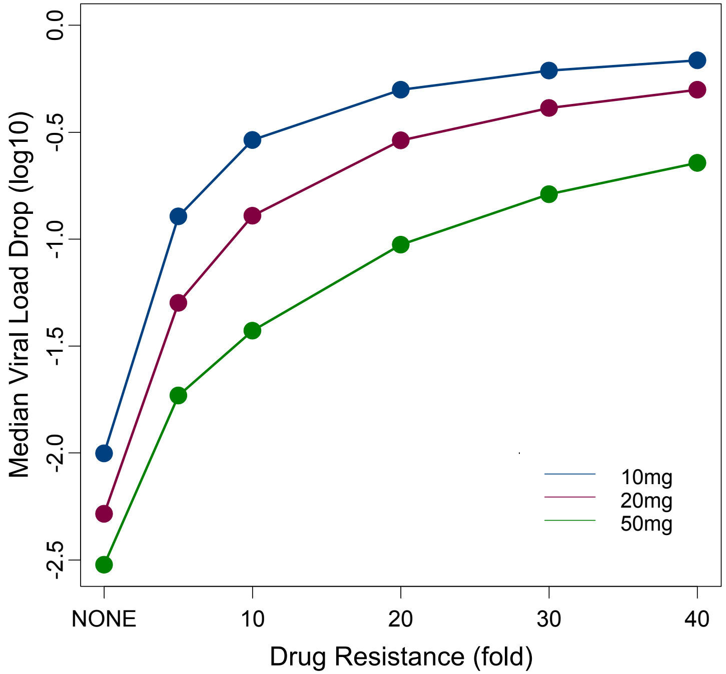


Simulation: Dose-Response in Patients with INI Resistance

Simulation Conditions:

- **Baseline characteristics of INI resistant patients were assumed similar to INI naïve patients**
- **Drug resistance to INI was introduced by**
  - **Up to 40-fold increase in IC50**
  - **Drug effect on latently infected cells reduced by 50%**
- **Dosing: 10, 20, 50mg QD**
- **End point: Viral load drop at Day 10**
- **Number of study replicates: 200**

INI Resistance Influences Antiviral Activity



Viral decline by 572 is influenced by the degree of resistance to INI

Conclusions

- PK of 572 is best characterized by a 2-compartment model with moderate inter-subject variability and relatively small residual errors.
- PK-viral dynamic model adequately described the effect of 572 on viral load in HIV-infected patients.
- The best fit model indicates 572 may act on additional mechanism in HIV life cycle, supporting the potent antiviral activity with 572.
- This model was used to guide dose selection in Phase 2b study (Ivy Song Abstract 50).