Pharmacokinetic-Pharmacodynamic Modeling & Simulation of the Virologic Response of Dolutegravir in HIV-Infected Patients with Integrase Inhibitor Resistant Virus

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Dolutegravir (TIVICAY™)

- HIV-1 integrase strand transfer inhibitor (INI)
  - 50 mg QD: Treatment-naive or treatment-experienced INI-naive
  - 50 mg BID: INI-experienced with certain INI-resistant mutations
  - Food increases exposure but may be taken without regard to meals
- Q148 mutation associated with lower susceptibility to DTG
- VIKING studies showed reduced efficacy in patients with Q148 + 2 or more additional INI-resistant mutations
- Objectives
  - Develop exposure-response model and identify significant predictors of antiviral response
  - Use model-based simulation to predict the antiviral response of various dosing scenarios which could increase or decrease DTG exposures in overall INI-resistant population and the subpopulation harboring Q148.

Eron et al., *(2013) J Infect Dis* 207:740-748; Castagna et al.,(2014) *J Infect Dis* 210:354-362; Akil et al., (2014) *Antivir Ther*. Doi: 10.3851/IMP2878.

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Methods

- Logistic regression modeling of VIKING/VIKING-3/VIKING-4
  - Probability of being a responder (Snapshot/TLOVR HIV RNA < 50 c/mL at Week 24) as a function of plasma DTG exposure (linear and Emax)
  - Both C_{min} and C_{avg} used as a measure of plasma exposure
  - Various covariates tested
- Simulations
  - Higher dose and co-administration with food
  - Co-administration with moderate-strong enzyme inducers
  - Co-administration with metal cation-containing vitamin supplements
- Modeling & simulations conducted using NONMEM

Summary of Subject Characteristics

Characteristics (Units)		VIKING (N=51)	VIKING-3 (N=183)	VIKING-4 (N=13)	Total N=247
Age (years)		47 [19-68]	48 [19-67]	49 [19-66]	48 [19-68]
Baseline CD_4 (cell count /mm^3)		122 [19-729]	140 [19-1100]	165 [19-525]	150 [19-1100]
Baseline Viral Load (HIV-1 RNA copies/mL)		4.31 [2.64-6.06]	4.38 [1.69-7.37]	4.41 [2-5.03]	4.38 [1.69-7.37]
Baseline Mutation Category [N(%)]	No Q148	27 (52.9)	126 (68.9)	5 (38.5)	158 (64)
	Q148+1	14 (27.5)	36 (19.7)	6 (46.2)	56 (22.7)
	Q148+≥2	10 (19.6)	21 (11.5)	2 (15.4)	33 (13.4)
Use of Metal Cation-Supplements [N(%)]	No	44 (86.3)	157 (85.8)	10 (76.9)	211 (85.4)
	Yes	7 (13.7)	26 (14.2)	3 (23.1)	36 (14.5)
Background ART Includes Inducers [N(%)]	No inducer	19 (37.3)	29 (15.8)	2 (15.4)	55 (22.3)
	Mild Inducer	27 (52.9)	144 (78.7)	9 (69.2)	175 (70.9)
	Mod-Strong	5 (9.8)	10 (5.46)	2 (15.4)	17 (6.9)

Values are median [range] unless otherwise indicated

No Q148: Includes Y143, N155H, T66, E92Q mutations, or historical evidence of resistance

Q148 + 1: Q148H/K/R with one mutation of G140A/C/S. L741I, E138A/K/T

Q148 + >=2: Q148H/K/R with two or more mutations of G140A/C/S, L741I, E138A/K/T

PKPD Model

$$Logit = 0.698 - 1.08*(BVL - 4.38) - INIMC + 0.00429*(BCD4 - 150) + 0.230*C_{min} + \eta_{Int}$$

- C_{min} or C_{avg} equally good predictors of Week 24 response
- Significant covariates
  - Baseline HIV-1 RNA (BVL)
  - Baseline mutation category (INIMC)
    - INIMC=0 (No Q148); 1.45 (Q148 + 1); 2.65 (Q148+ ≥2)
  - Baseline CD4 cell count (BCD4)
- Non-significant covariates
  - Prior use of raltegravir/elvitegravir or duration of prior INI treatment
  - Phenotypic Susceptibility Score (PSS) of optimized background therapy
  - Genotypic Susceptibility Score (GSS) of optimized background therapy
  - HIV Risk Factor
  - CDC Category

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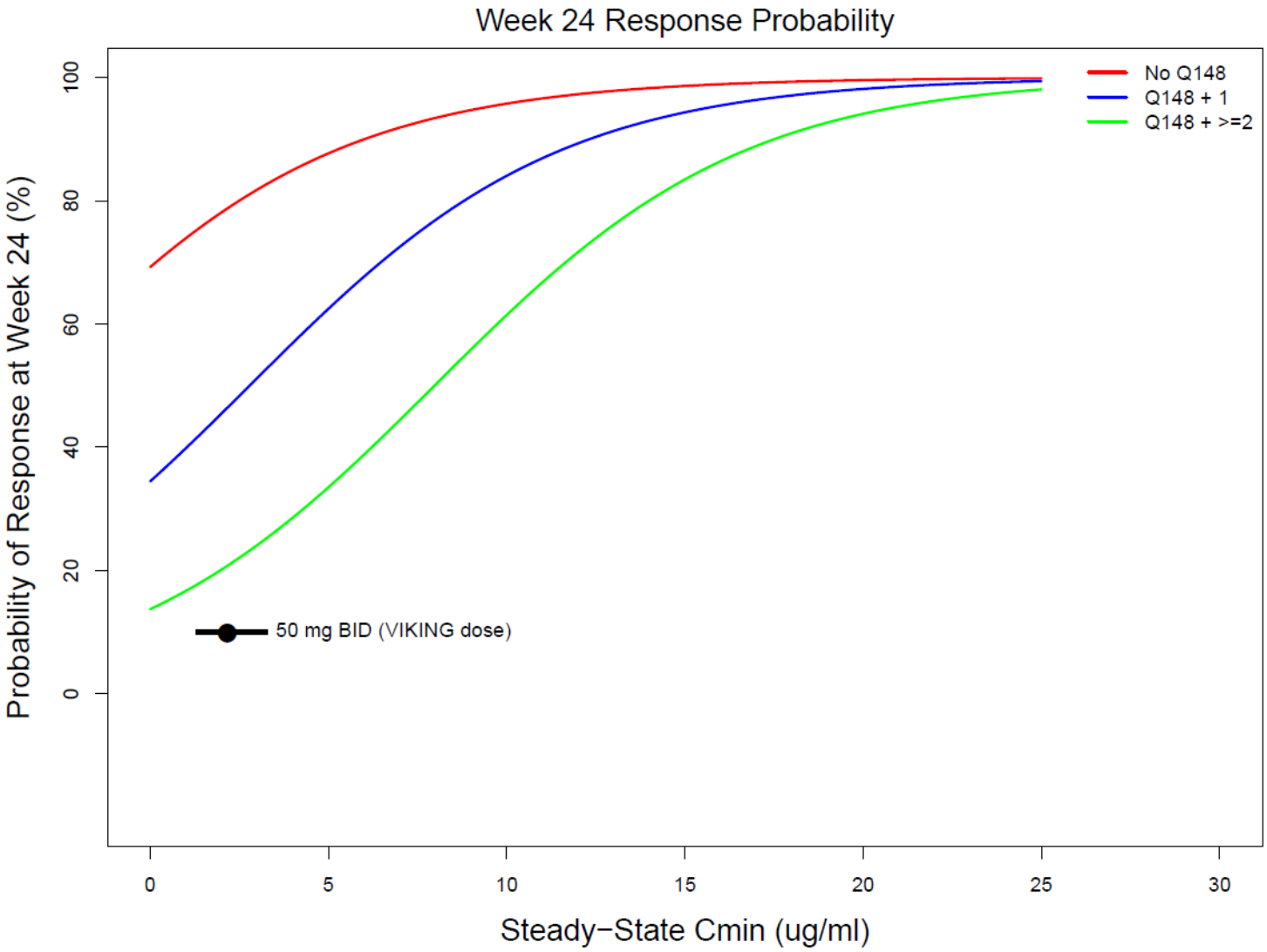
Validation: Model Adequately Reflects Observed Data at Week 24

Baseline INI Mutation Category	Observed Response Rate (%)	Mean Predicted Response Probability (%)	
		C_{min} Model	C_{avg} Model
Overall (n=220)	68.6	67.0	67.0
No Q148 (n=143)	80.4	77.7	77.7
Q148 + 1 (n=51)	56.9	57.9	57.8
Q148 + ≥ 2 (n=26)	26.9	25.7	25.8

Response is defined as the proportion of subjects with HIV-1 RNA < 50 copies/mL as defined by the TLOVR (VIKING) or Snapshot (VIKING-3, VIKING-4) algorithms

C_{min}-Week 24 Response by Mutation Category



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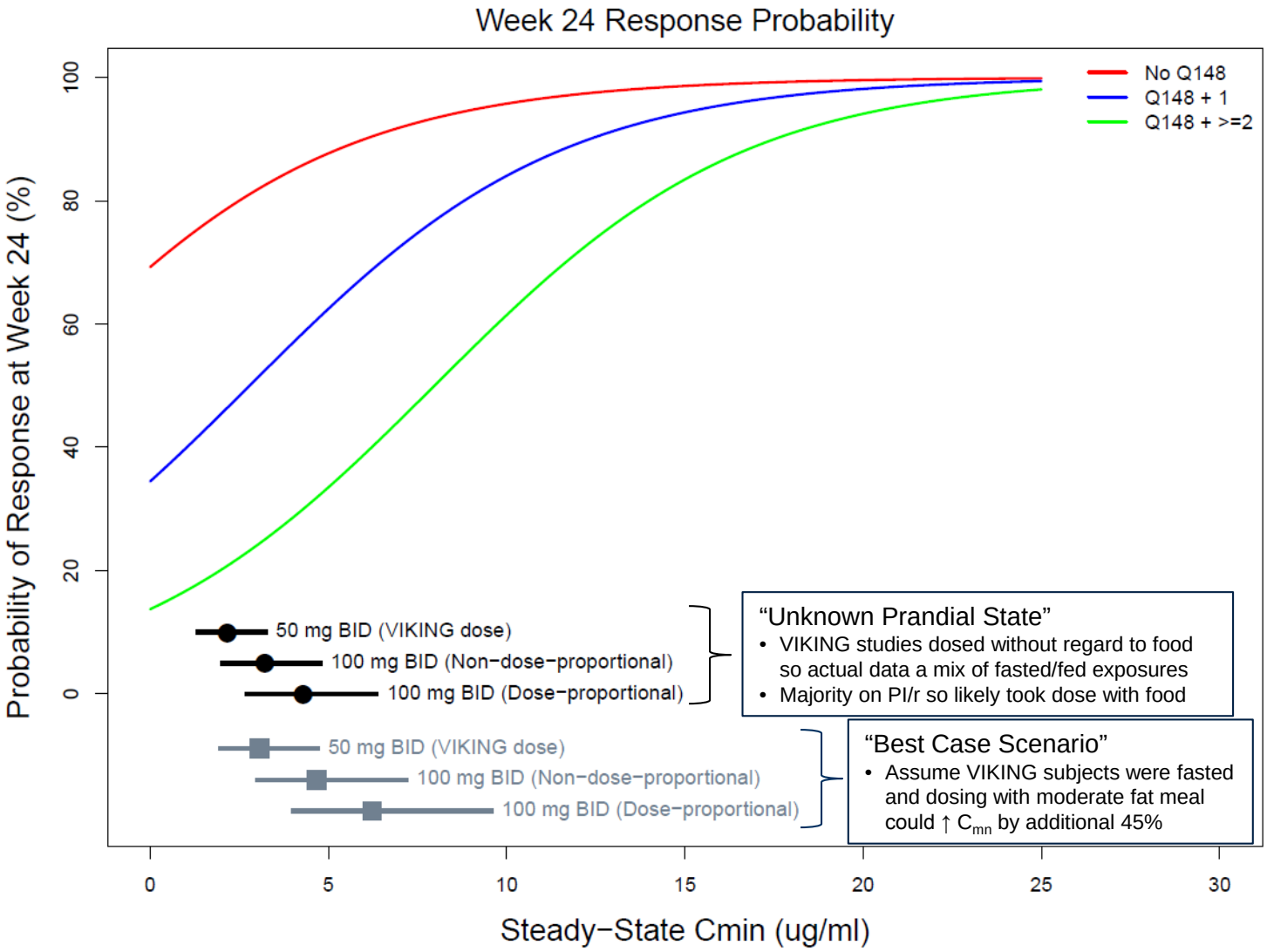
C_{min}-Week 24 Response by Mutation Category



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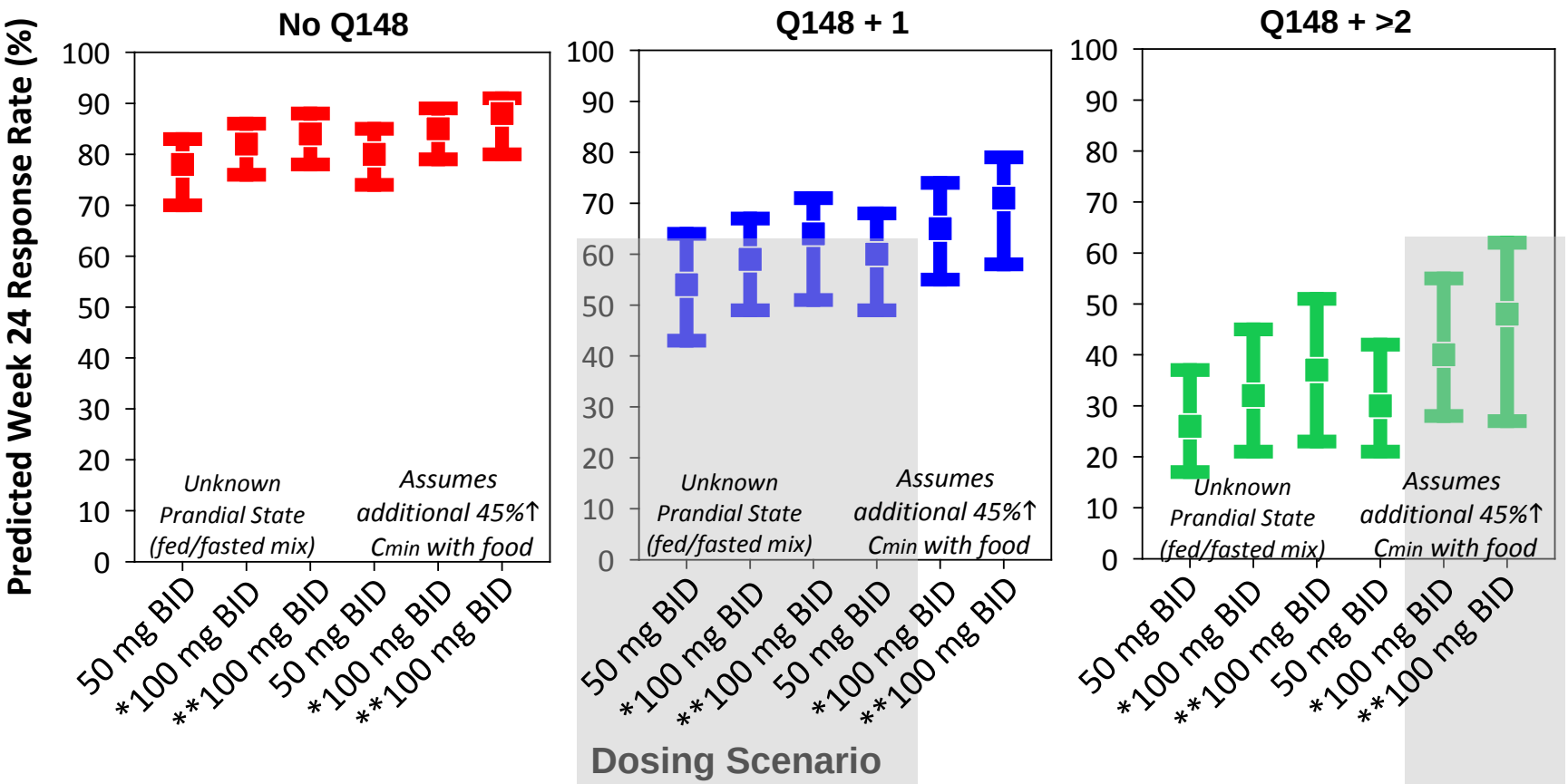
Simulations: Effect of Higher Dose and Food



*Assumes less than dose-proportional PK; i.e., 1.75-fold higher C_{min} for 100mg BID vs. 50mg BID, based on prior clinical pharm study.

**Assumes dose-proportional PK; i.e., 2-fold higher C_{min} for 100mg BID vs 50mg BID.

Simulation results of 200 replicates of each cohort (N=1000) for each mutation category and regimen

Mean and 5th, 95th confidence interval presented

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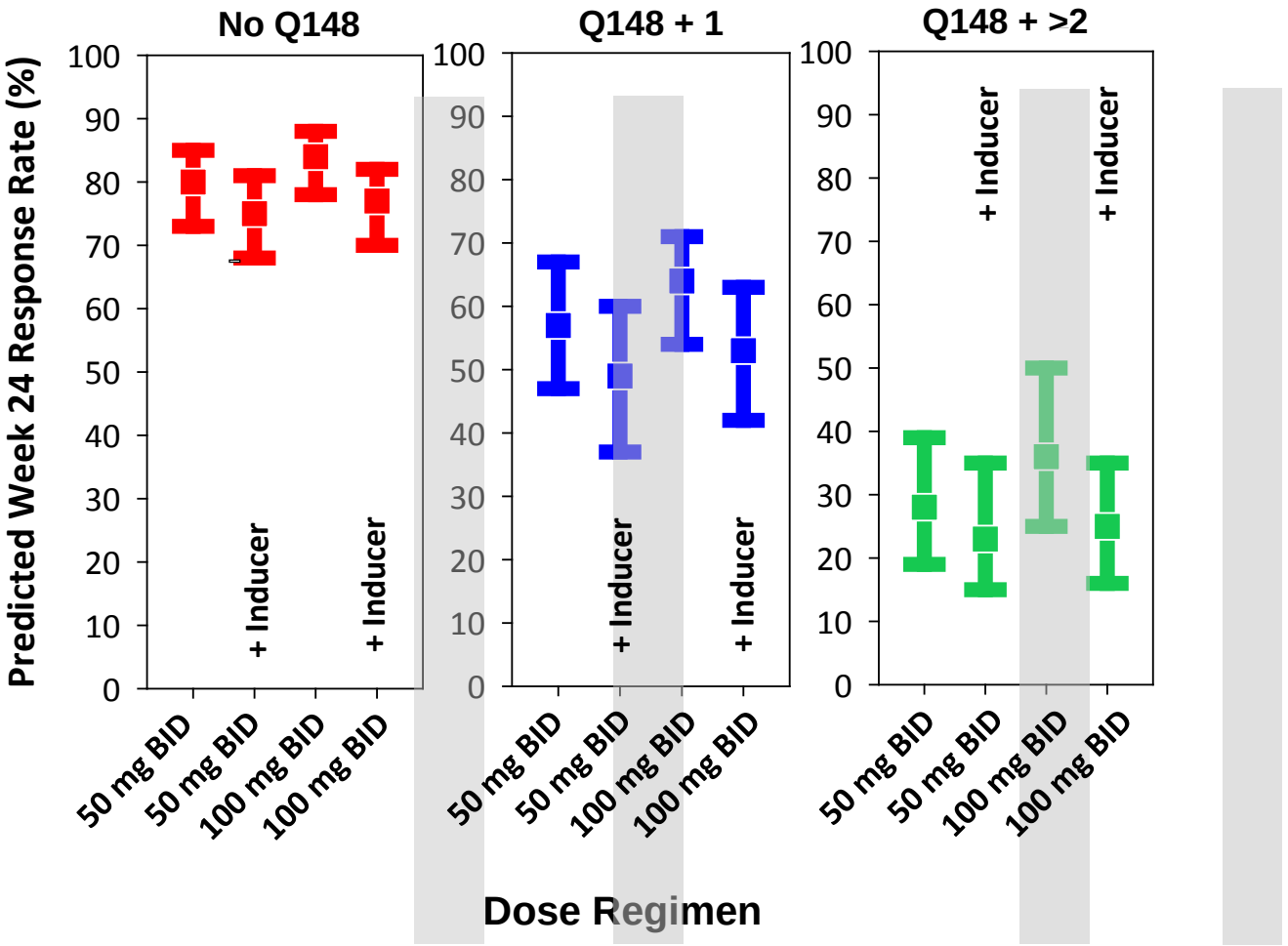
Simulations:
Effect of Moderate-Strong Enzyme Inducers



Simulation results of 200 replicates of each cohort (N=1000) for each mutation category and regimen
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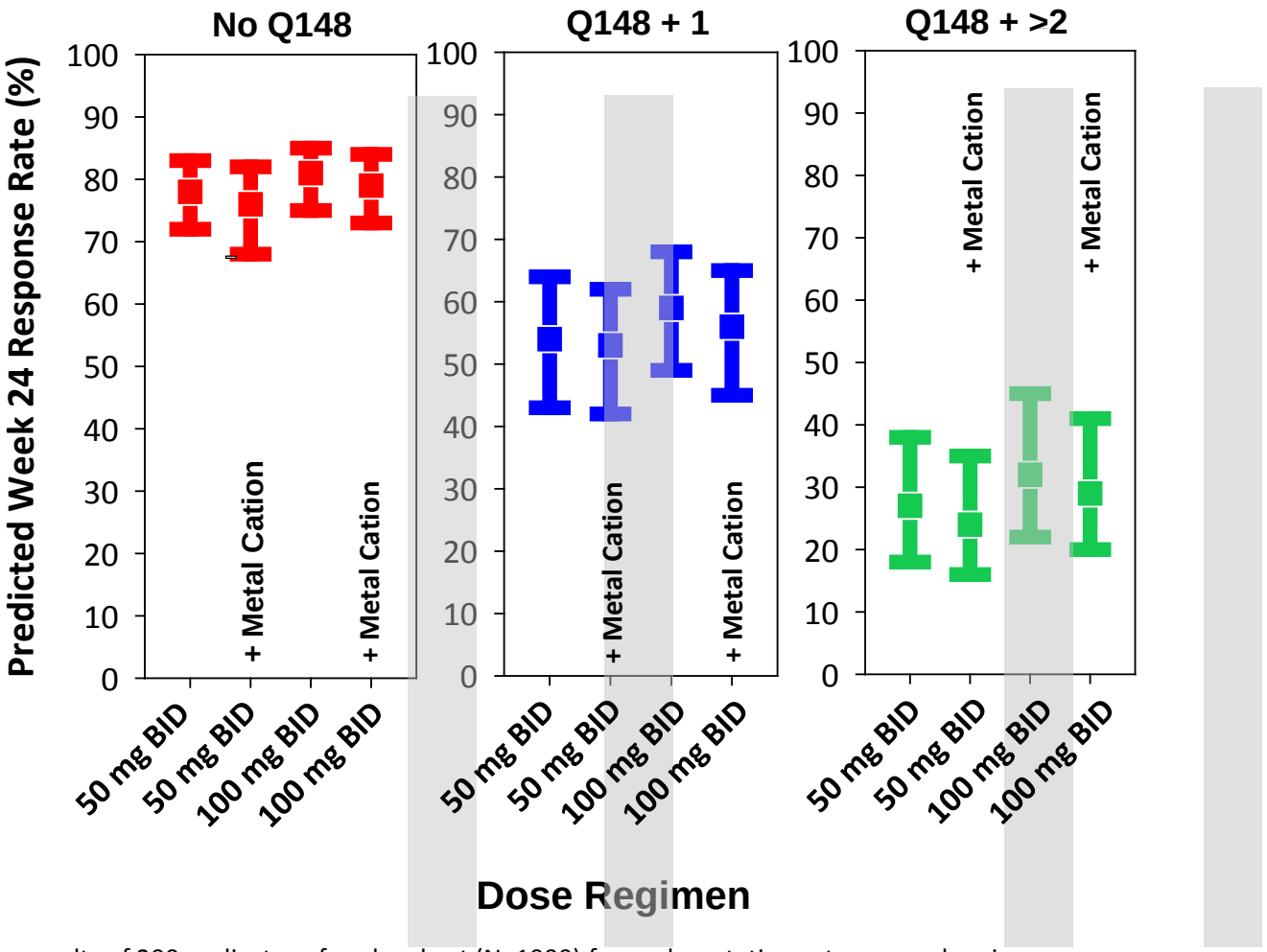
Simulations:
Effect of Metal Cation-Containing Supplements



Simulation results of 200 replicates of each cohort (N=1000) for each mutation category and regimen
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Conclusions

- DTG concentration (C_{min} or C_{avg}) is a predictor of long-term response. Other predictors include baseline mutation category, baseline HIV-1 RNA, and baseline CD4.
- Modeling and simulations support the current recommendation of 50 mg BID in the majority of the INI-resistant patient population.
- Simulations confirmed the current recommendations for dosing with moderate-to-strong enzyme inducing drugs or metal cation-containing vitamin supplements.

Acknowledgments

- Investigators, staff & patients of VIKING, VIKING-3 & VIKING-4