Impact of HR1 Enfuvirtide Resistance Mutations on Sensitivity to HR2 Directed Neutralizing Antibodies

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Trimeris

Fuzeon (Enfuvirtide)

- First in class HIV entry inhibitor
- Derived from HR2 region of gp41 and binds HR1
- ENF resistance mutations seen primarily in aa 36-45 of gp41

Two of the most broadly neutralizing antibodies target the MPER region of gp41

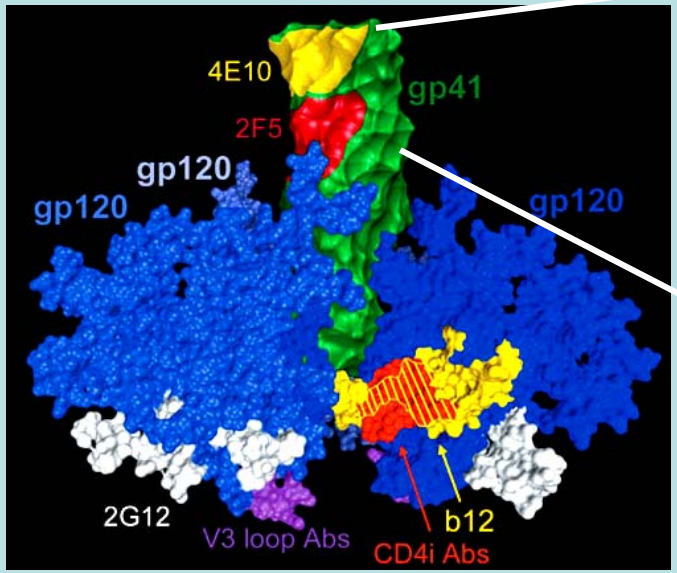


Figure 1 Burton *et al*., Nat. Immunol., 2004

The HIV-1 Envelope

2F5 and 4E10 bind to the gp41 HR2 domain, at sites within or near the sequence used to derive ENF.

2F5 core **4E10 core**

QNQQEKNEQELLELDKWASLWNWFDITNWLWYIKIFIMI

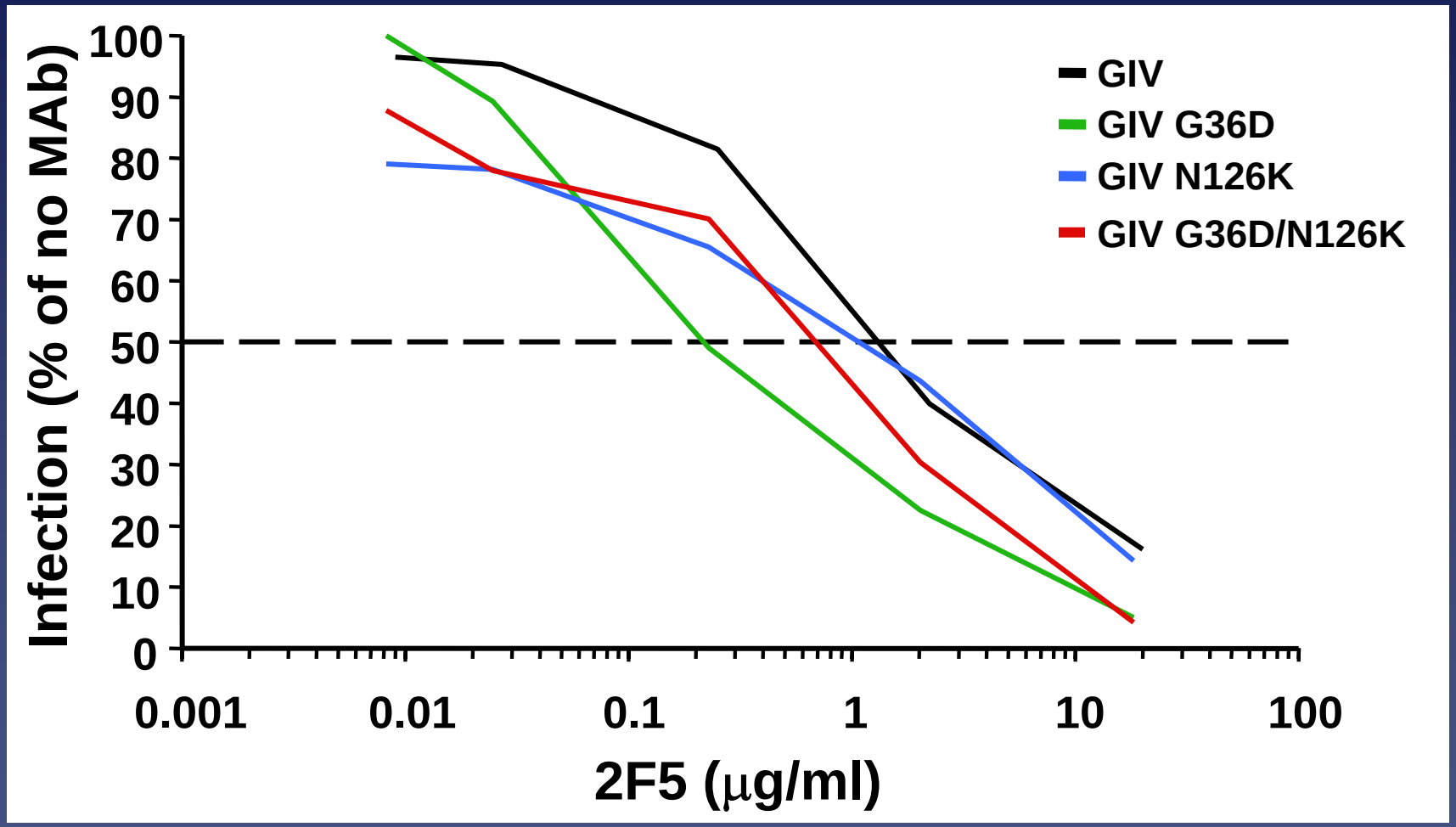
YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF Enfuvirtide

Enfuvirtide Resistance Mutations: Impact on Human Immunodeficiency Virus Envelope Function, Entry Inhibitor Sensitivity, and Virus Neutralization

Jacqueline D. Reeves et. al
Journal of Virology, Apr 2005

- **LAI and YU-2 with ENF resistance mutations G36D and V38M are more sensitive to neutralizing antibodies 2F5 and 4E10 than wild type LAI and YU-2.**
- **These mutations increase sensitivity of LAI to neutralization by sera from HIV-infected patients.**
- **Hypothesize that these HR1 mutations (without compensatory HR2 mutations) make these key epitopes more exposed or more available to neutralizing Abs.**

Effect of G36D Resistance Mutation in GIV on Sensitivity to 2F5



No change in neutralizing antibody sensitivity seen in 098 background

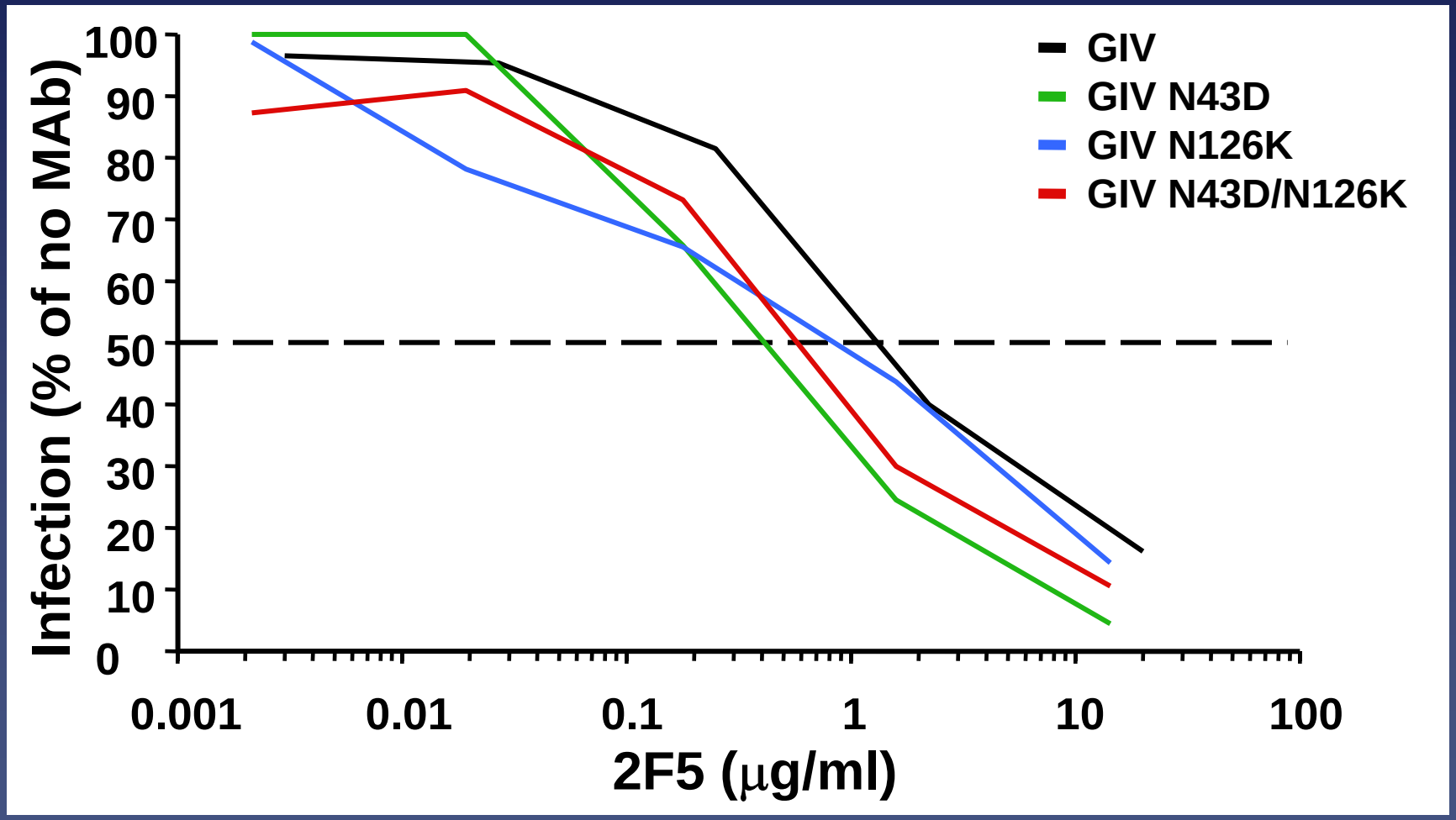
Genotypic Changes on Enfuvirtide Treatment in gp41 aa36-45

Substitution	N*	Percent
V38A	35	12.2
N43D	20	7
G36D	10	3.5
V38M	10	3.5

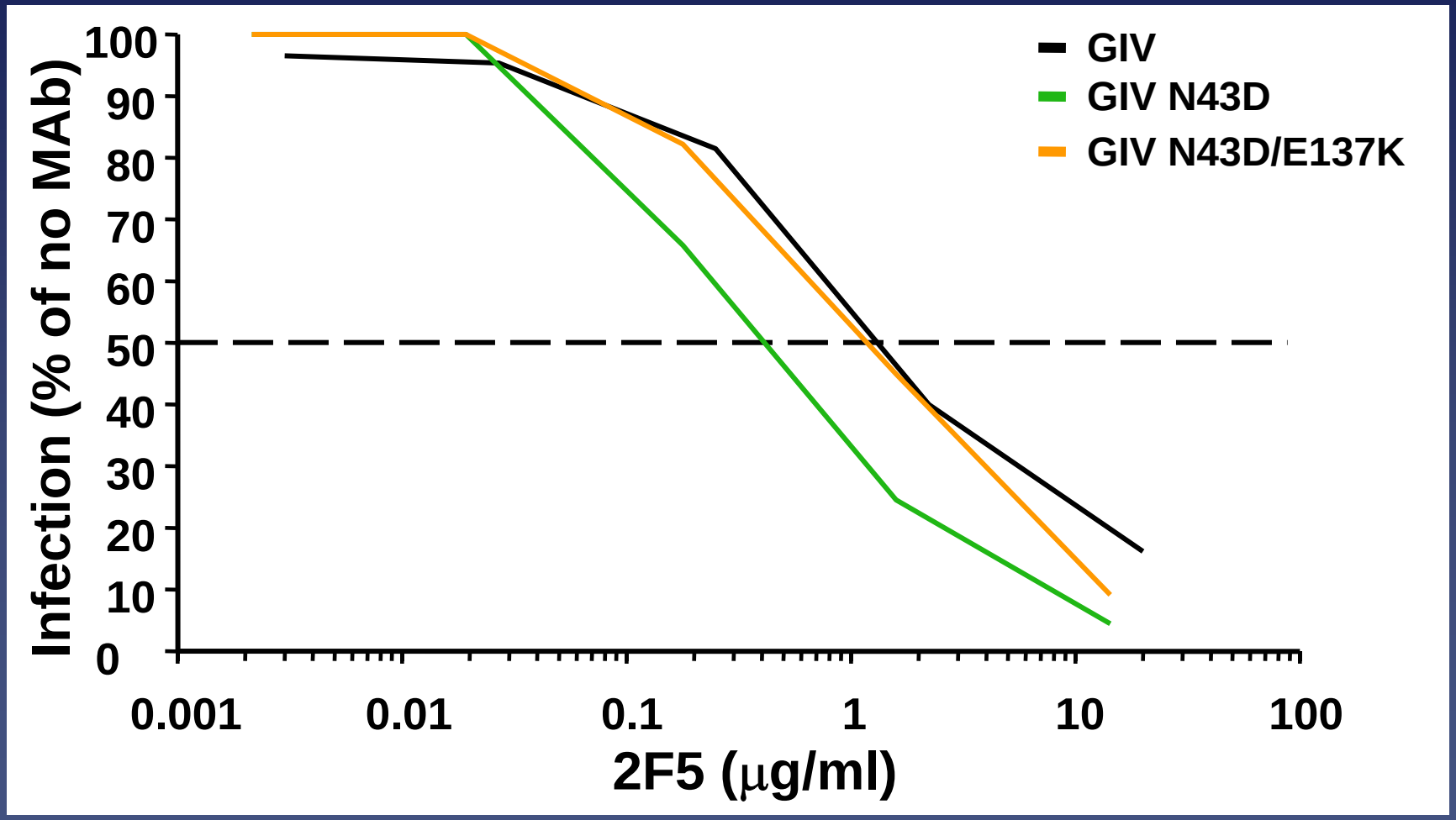
Derived from TORO trial week 48 study report

*Out of 287 patients achieving VF status by week 48

Effect of N43D HR1 and Compensatory HR2 mutations in GIV on 2F5 Neutralizing Ab Sensitivity



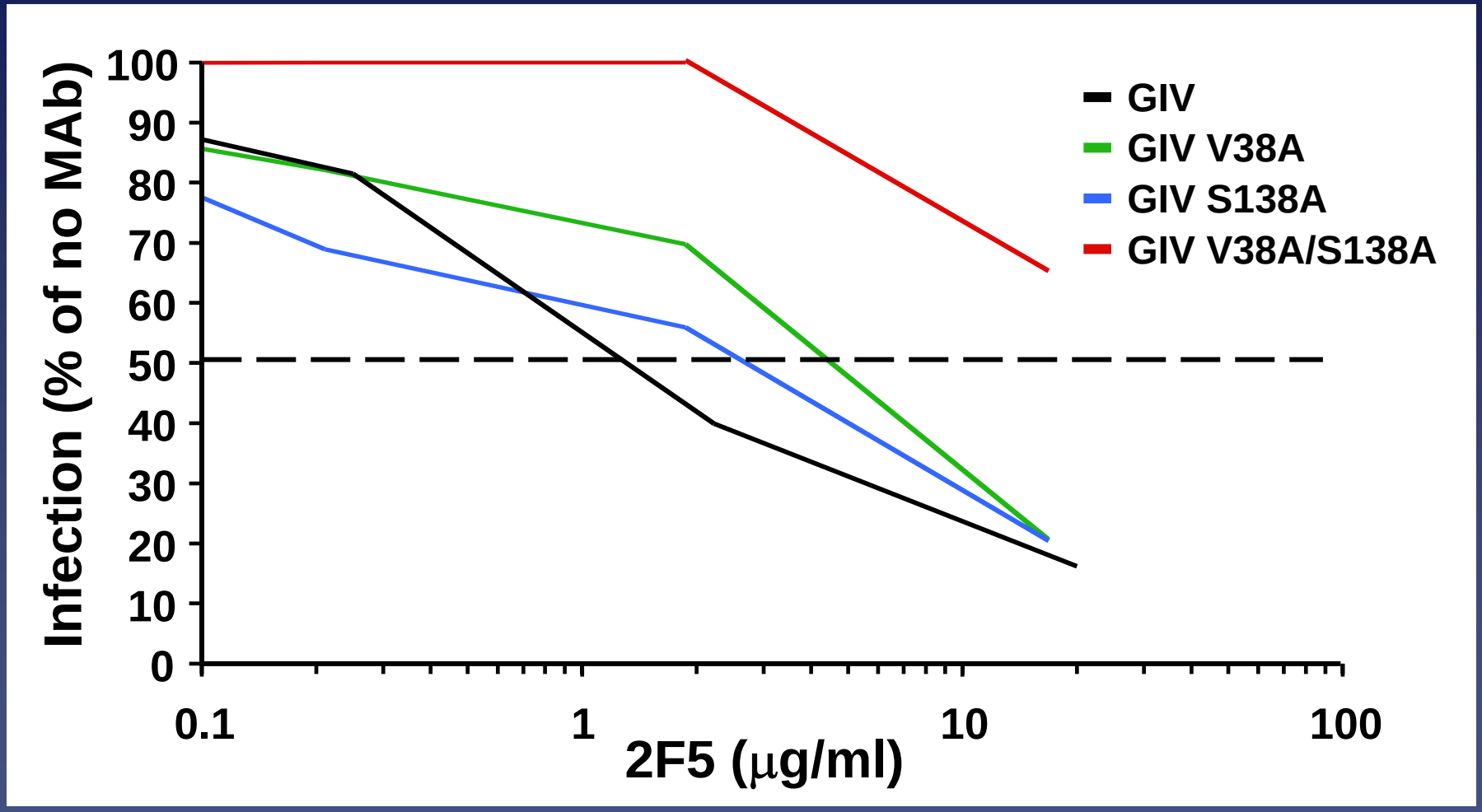
Effect of N43D HR1 and Compensatory HR2 mutations in GIV on 2F5 Neutralizing Ab Sensitivity



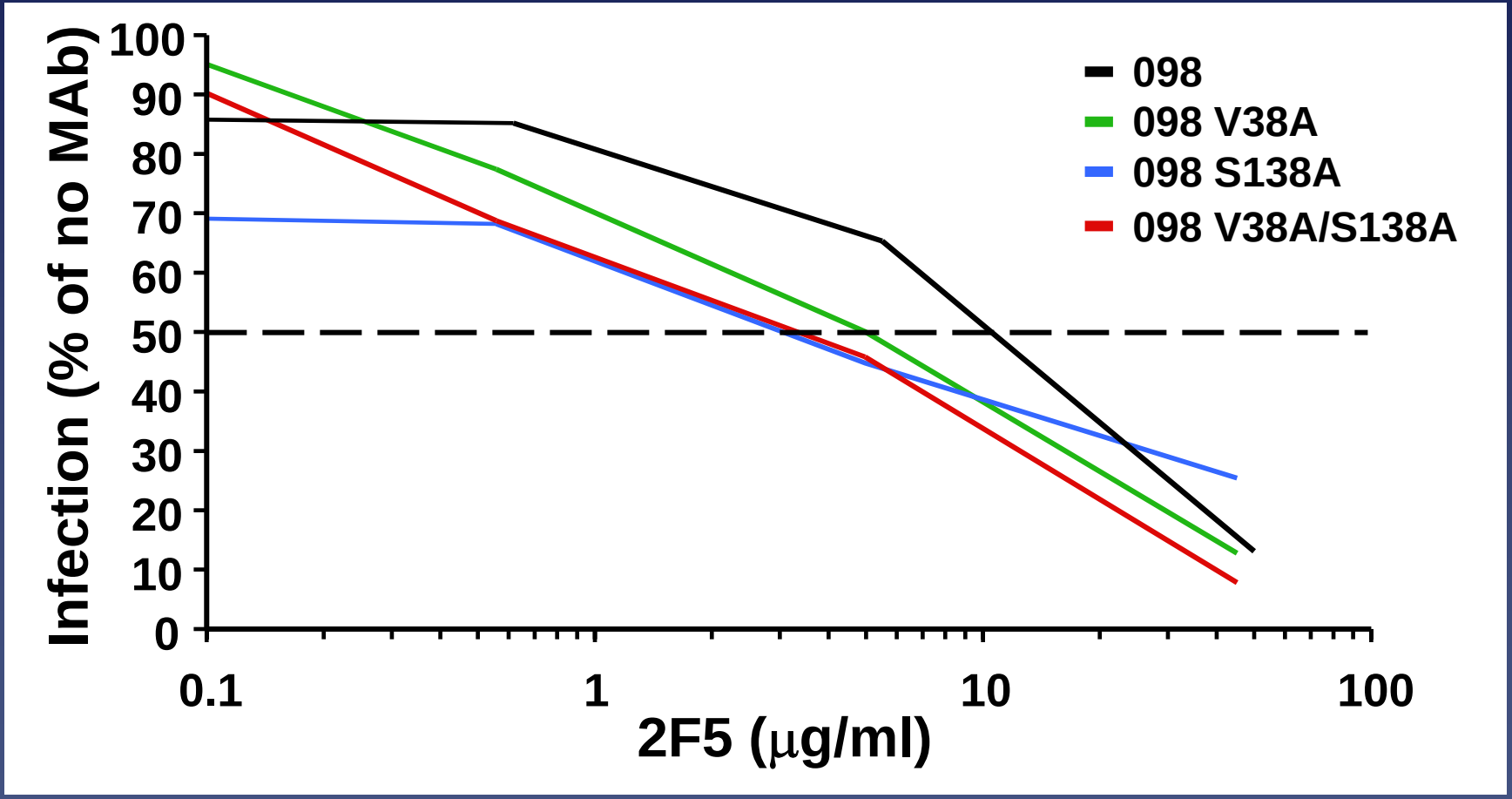
Effect of N43D HR1 and Compensatory HR2 mutations in a Primary Isolate (098) on 2F5 Neutralizing Ab Sensitivity

	FC Increase Neutralization Sensitivity	FC Resistance
	2F5	Fuzeon
098 N43D	2.5	2.6
098 N126K	0.2	2.5
098 S138A	1.2	0.7
098 N43D/N126K	0.6	3.3
098 N43D/S138A	0.8	2.2

HR1 Fuzeon Resistance Mutation V38A in GIV Confers a Loss of 2F5 Neutralizing Sensitivity



Effect of HR1 Fuzeon Resistance Mutation V38A on 2F5 Neutralizing Sensitivity is Background Dependent



Conclusions

- ENF HR1 resistance mutations alter sensitivity to HR2 directed neutralizing antibodies.
  - In most cases, HR1 mutations lead to an increase in sensitivity.
  - In some cases, HR1 mutations result in a loss of sensitivity.
- In most cases HR2 mutations lessen the effect of HR1 mutations on neutralization sensitivity.
- The increased sensitivity to neutralizing antibodies may have implications for viral fitness of ENF resistant viruses.
- This data is consistent with the hypothesis that ENF resistance mutations alter the kinetics of HR1-HR2 interactions and lifetimes of fusion intermediates.

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