

Resistance and Cross-Resistance to First Generation Integrase Inhibitors: Insights from a Phase 2 Study of Elvitegravir (GS-9137)

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Abstract #9

Elvitegravir (EVG, GS-9137 / JTK-303)



- Dihydroquinoline carboxylic acid strand transfer inhibitor of HIV integrase (both HIV-1 and HIV-2)
- Serum-free antiviral $IC_{50} = 0.2$ nM; $IC_{90} = 1.2$ nM in PBMCs
- Active against NRTI-, NNRTI-, and PI-resistant isolates

Resistance to Elvitegravir (EVG) *In Vitro*: Two Primary Integrase Resistance Patterns¹

IN Mutation	Elvitegravir (EVG) Fold Change	Raltegravir (RAL) Fold Change
E92Q	33	6.0
T66I	15	1.4

- Secondary IN mutations observed
 - With E92Q: H51Y, S147G, E157Q
 - With T66I: F121Y, S153Y, R263K
 - Further reduce EVG susceptibility
 - F121Y also reduces RAL susceptibility

Study GS-183-0105: Active Control, Dose Ranging Phase 2 Study of EVG/r

278 patients
HIV RNA ≥ 1000 copies/mL
Any CD4 cell count
 ≥ 1 protease resistance mutation

OBT = NRTIs +/- T-20
NNRTIs not allowed in OBT
Stratified by T-20 use in OBT
PIs not allowed in EVG arms*

Comparator PI/r (n=63)

EVG/r 20 mg QD (n=71)

EVG/r 50 mg QD (n=71)

EVG/r 125 mg QD (n=73)

* Darunavir and tipranavir permitted after week 8 in EVG/r arms

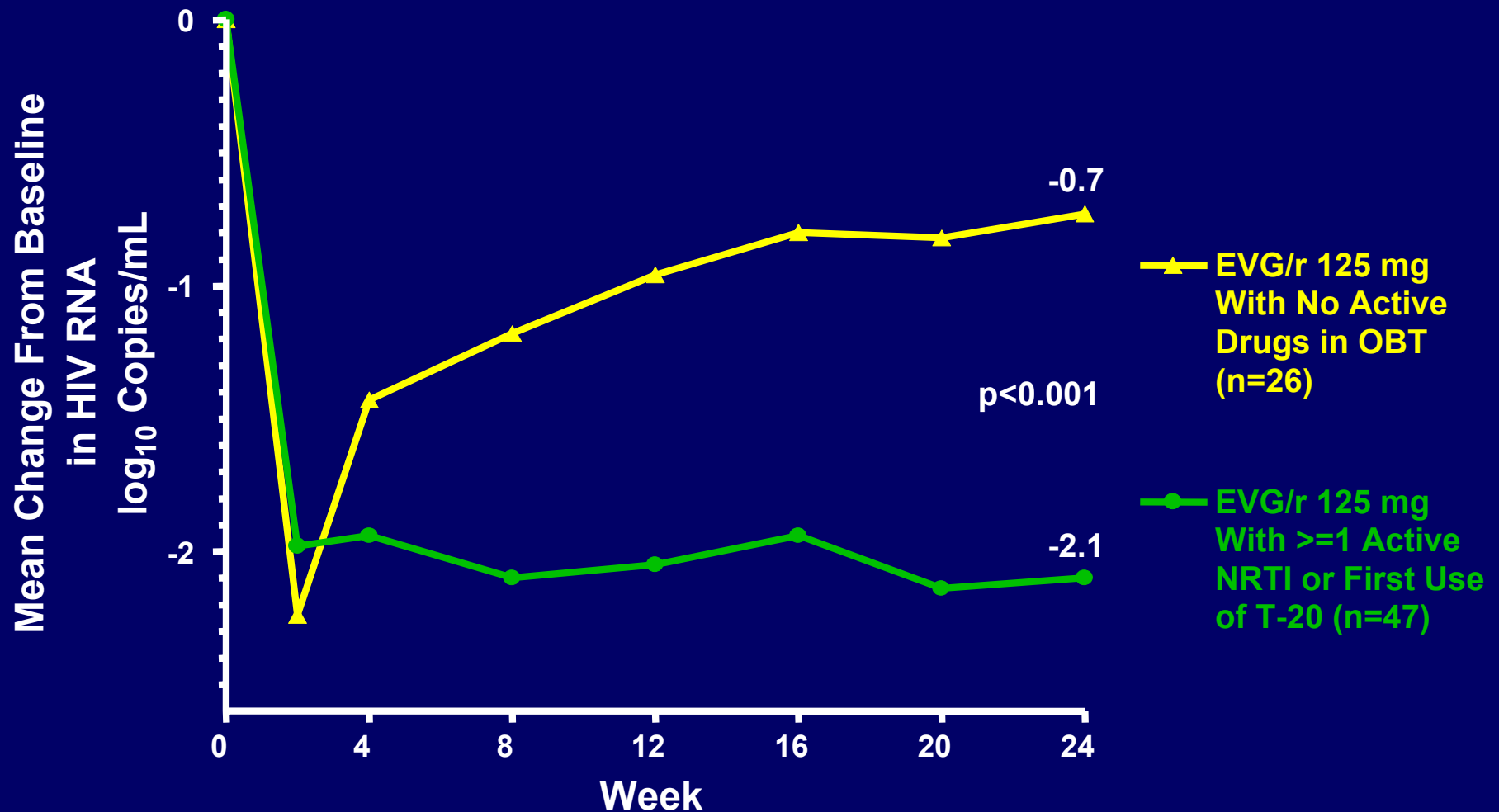
GS-183-0105 Baseline Characteristics

Baseline Parameters	CPI/r n=63	EVG/r 20 mg, n=71	EVG/r 50 mg, n=71	EVG/r 125 mg, n=73
Mean HIV-1 RNA, log ₁₀ c/mL	4.54	4.66	4.47	4.71
Mean CD4 cells/mm ³	158	180	243	157
Genotypic Sensitivity Score ^a , GSS=0 for all NRTIs in OBT	32 (51%)	35 (49%)	34 (49%)	35 (48%)
PI Resistance Mutations, Median #	11	11	10	11
First Use of T-20	12 (19%)	12 (17%)	17 (24%)	19 (26%)
ARVs in OBT, inc. T-20, Median #	3	3	3	3

a. GSS calculated using ANRS algorithm

Data from Zolopa et al 2007

Change from Baseline in HIV RNA with EVG/r 125 mg: Influence of Activity of OBT*

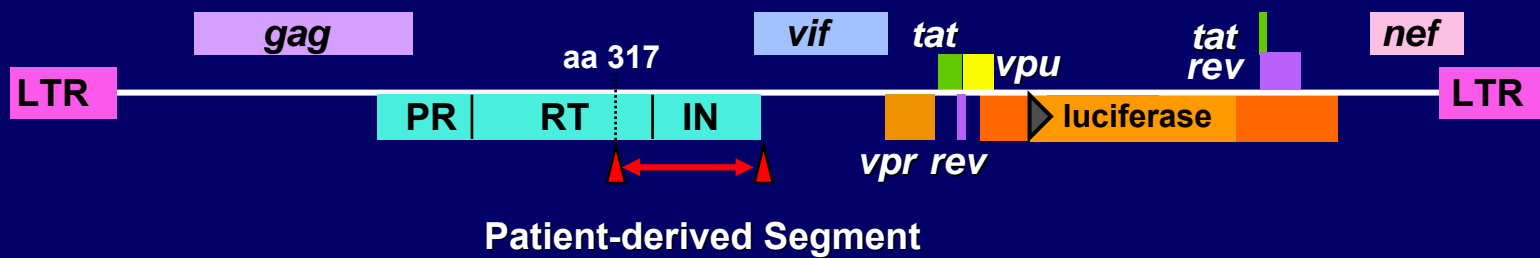


*Data from EVG/r 125 mg patients after addition of a PI were excluded

Data from Zolopa et al 2007

PhenoSense™ HIV for Integrase Inhibitors (INI): Monogram Biosciences

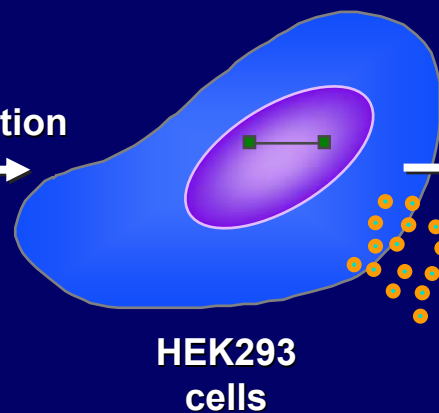
RHIN Resistance Test Vector



Resistance Test Vector DNA

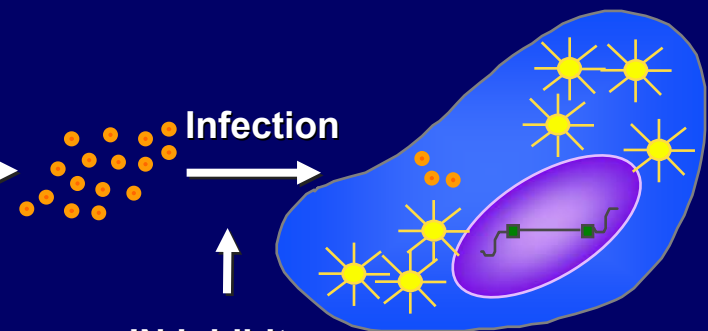


Transfection



Infection

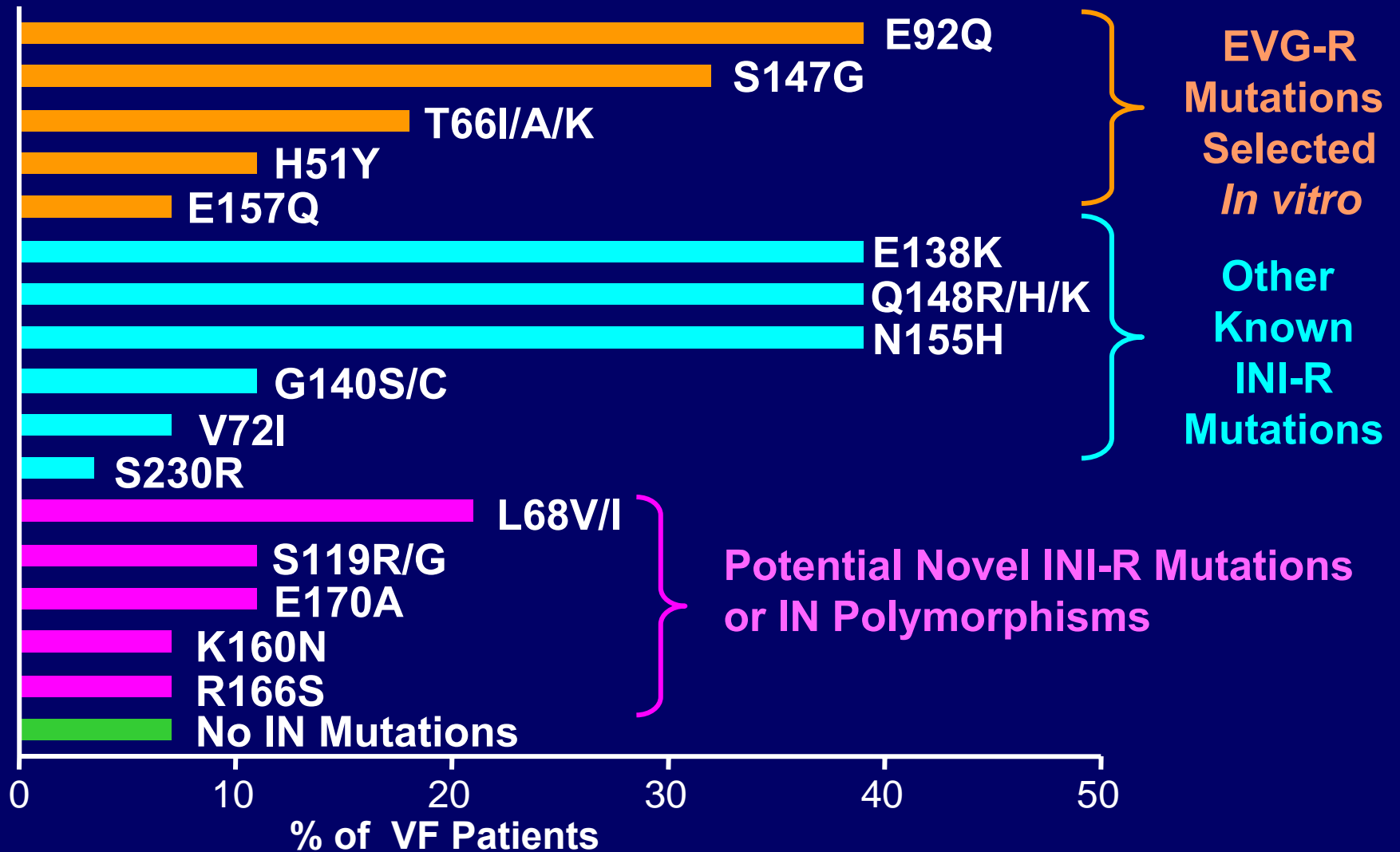
IN inhibitor



EVG/r 125 mg Virologic Failure (VF) Patients Analyzed for INI Resistance by Week 24

- **Patients in EVG/r 125 mg arm with protocol-defined VF by Week 24 were analyzed, n=30**
 - **Baseline and confirmed VF sample**
 - **IN genotype and INI phenotypes (blinded)**
 - **Median time > 400 c/mL before analysis: ~ 14 weeks**
 - **Median HIV-1 RNA log₁₀ c/mL at analysis: 4.8 (3.2 - 5.8)**
- **Baseline and VF IN genotype / INI phenotype, n=28**
 - **NL4-3 reference for GeneSeq and PhenoSense INI Assays**

IN Mutations Developing in EVG/r 125mg VF Patients by Week 24 (n=28)



IN Genotypic Patterns Developing in EVG/r 125 mg VF Patients (n=28)

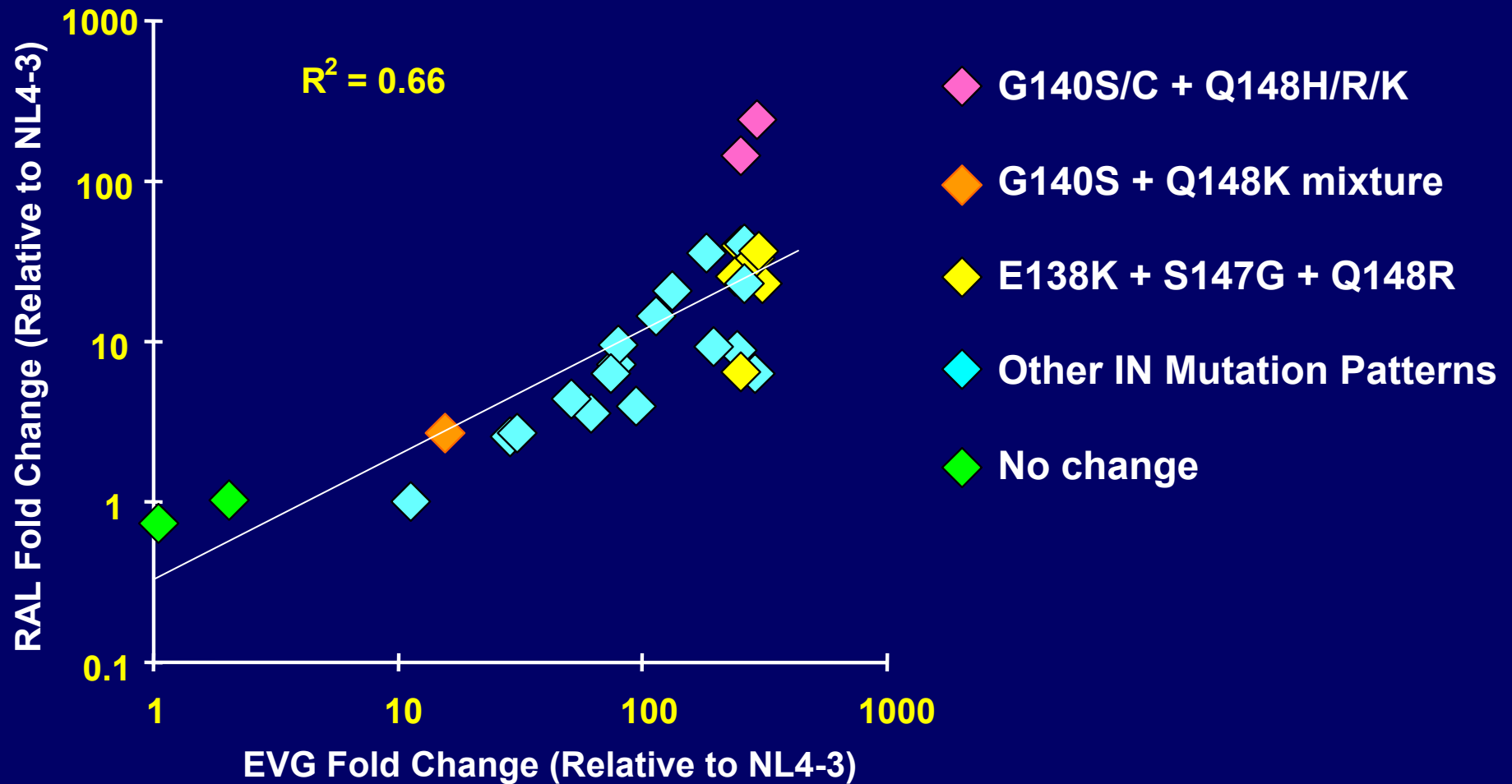
IN Genotypic Patterns (population sequencing)^{1,2}	N (%)
Any E92Q	11 (39%)
+ N155H (+/- other mutations)	4 (14%)
+ T66A (+ other mutations, no N155H)	3 (11%)
+ other mutations (no T66I/A/K, no N155H)	4 (14%)
Any N155H	11 (39%)
+ other mutations (no E92Q)	7 (25%)
+ T66I (+ other mutations, no E92Q)	1 (3.5%)
+ E138K (+ other mutations, no E92Q, no T66I)	3 (11%)
+ other mutations (no E92Q, no T66I, no E138K)	3 (11%)
E138K + S147G + Q148R (+/- other mutations)	6 (21%)
G140C/S + Q148R/H/K (+/- other mutations, inc T66K)	3 (11%)

1. Median number of IN mutations developing: n = 4 (range 0-9)
2. Mutations were frequently observed as mixtures and may not be present on the same viral genome; some patients classified in > 1 group.

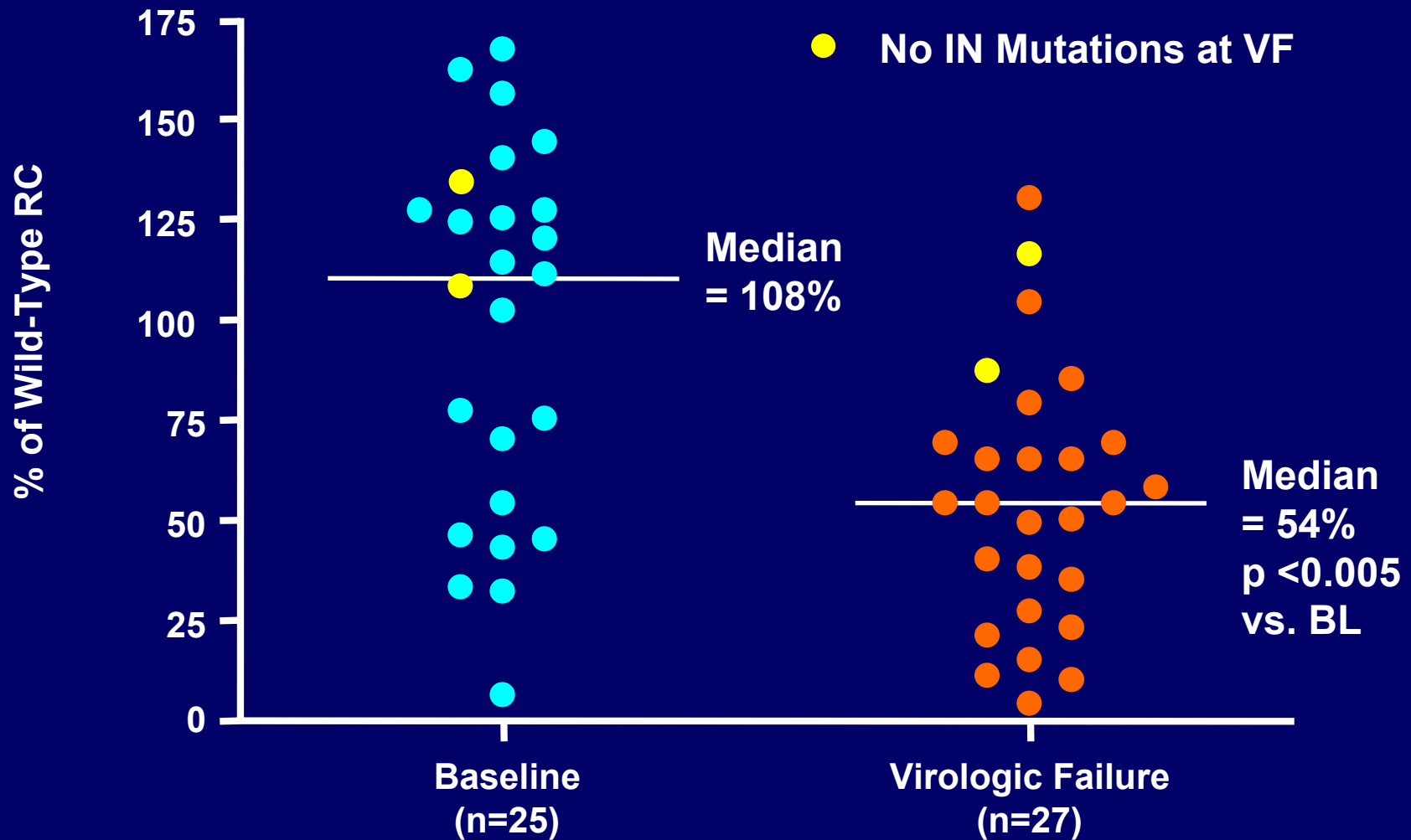
INI Phenotypic Analysis of HIV-1 from EVG/r 125 mg VF Patients (n=28)

Phenotypic Parameters	Fold Change (Relative to NL4-3)
EVG at Baseline: Mean	1.50 ±0.45
Median (Range)	1.42 (0.91 - 2.53)
EVG at EVG VF: Mean	> 151¹
Median (Range)	152 (1.02 - 301)
RAL at EVG VF: Mean	> 28¹
Median (Range)	10 (0.78 - >256)

Correlation of EVG and RAL Susceptibility Among EVG/r VF Isolates (n=28)



IN Replication Capacity at Baseline and VF on EVG/r 125 mg



Conclusions (I)

- In highly treatment-experienced patients, treatment with 125 mg EVG/r and at least one additional active NRTI or T-20 resulted in a sustained $>2 \log_{10}$ reduction in HIV-1 RNA through 24 weeks
- Common IN mutation patterns at failure included:
 - **E92Q + other mutations**
 - **N155H + other mutations**
 - **Q148R/H/K + other mutations**
 - These patterns overlap with the two major resistance patterns reported in raltegravir clinical trials (N155H + others; Q148K/R/H + others)

Conclusions (II)

- Development of IN mutations was associated with reduced susceptibility to both EVG and RAL
 - Clinical cutoffs for both drugs remain to be established
 - Potential for drug sequencing within the class is unknown
- Development of IN mutations was associated with significant reductions in viral replication capacity
 - Clinical significance of IN RC reduction is unknown

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