

Longitudinal Analysis of Resistance to the HIV-1 Integrase Inhibitor Raltegravir: Results from P005 a Phase 2 Study in Treatment Experienced Patients

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Phase 2 Protocol 005 (treatment-experienced)

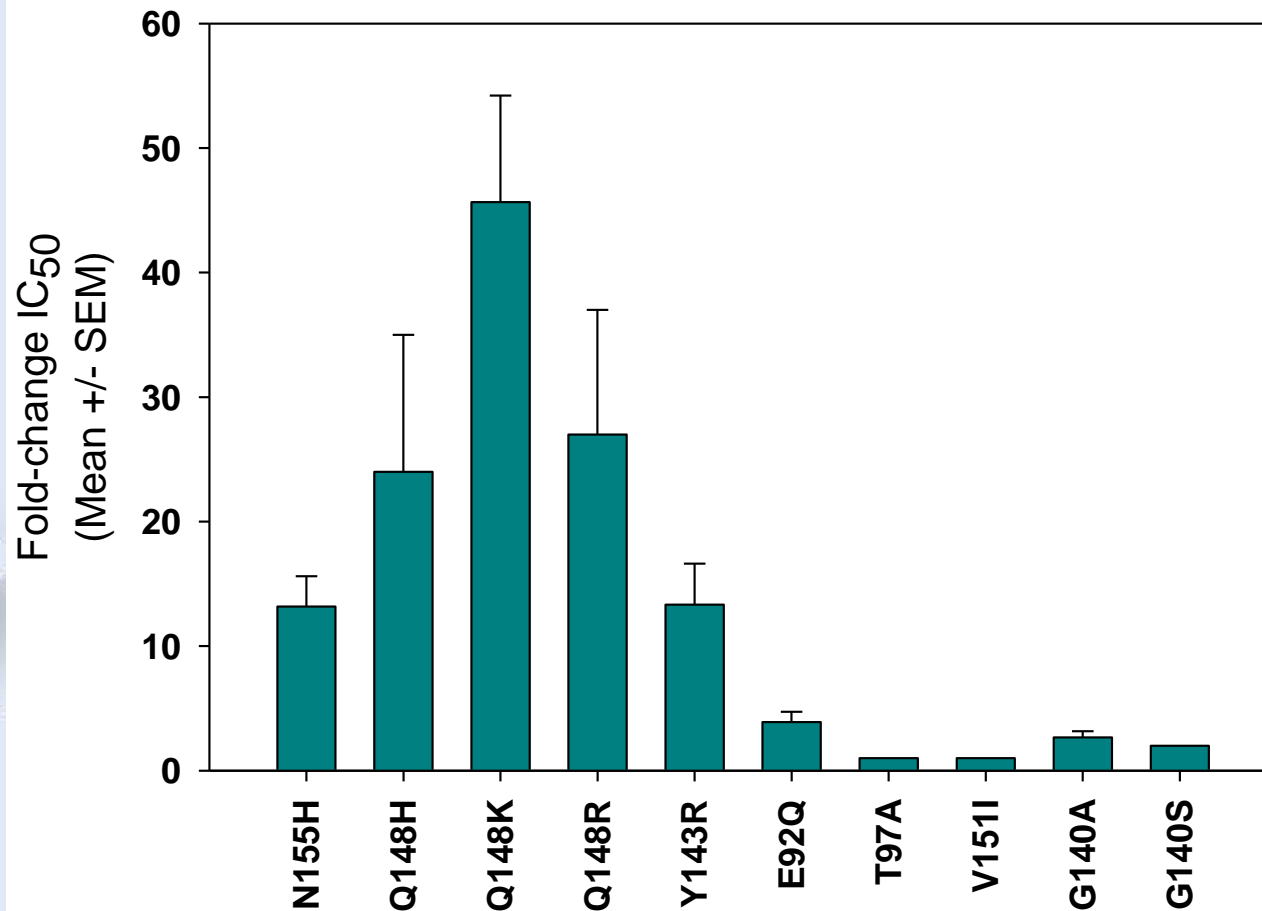
- ◆ **Patients with 3-class-resistance received Optimized Background Therapy (OBT) + raltegravir (200, 400, or 600 mg b.i.d.) or OBT + placebo (Grinsztejn, et al., 2007, Lancet 369:1261)**
- ◆ **48 week efficacy: Virologic failure observed in 38/133 (28.6%) patients on RAL**
- ◆ **Initial resistance analysis (cross-sectional): Integrase signature mutations were observed in 35 of 38 patients failing RAL, usually with other mutation(s)**
- ◆ **Summary of phenotypic data (see poster)**
 - Signature mutations (N155H, Q148H/K/R) confer >10-fold RAL resistance and reduce replication capacity
 - Secondary mutations consistently augment resistance, but have inconsistent effects on replication capacity
 - Q148 pathway has higher resistance than N155 pathway

Original genotype analysis of raltegravir resistance in PN005 (48 week VFs)

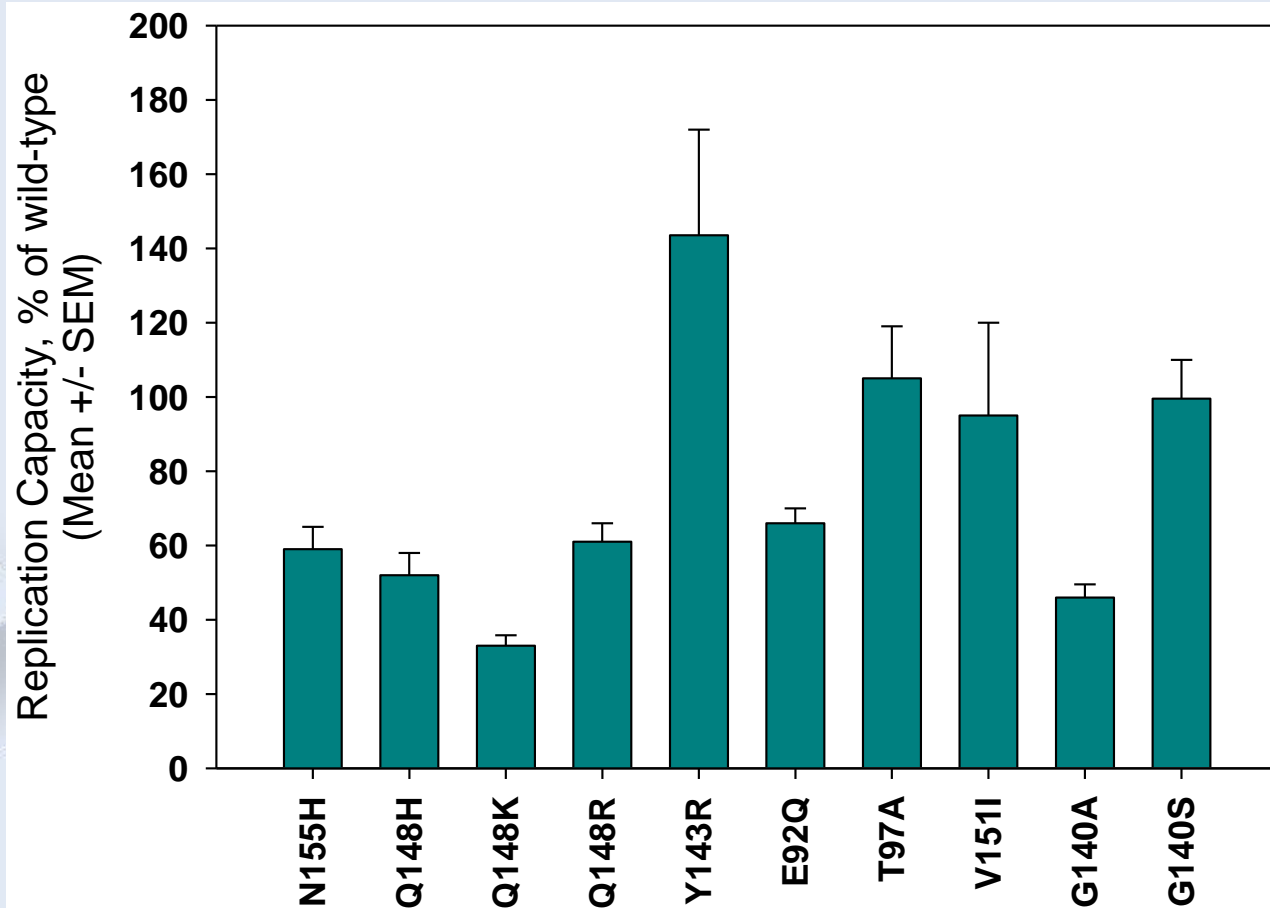
| N155H pathway | Q148 pathway |
|--------------------------------------|-------------------------------------|
| Total N = 14 | Total N = 20 |
| N155H (n = 2) | Q148H, G140S (N=13) |
| N155H, L74L/M (n = 1) | Q148R (n = 1) |
| N155H, E92Q (n = 1) | Q148R, G140S (n = 2) |
| N155H, T97A (n = 3) | Q148K, E138K (n = 1) |
| N155H, Y143H (n = 1) | Q148R, E138E/K (n = 1) |
| N155H, V151V/I, G163K (n = 1) | Q148R, L74L/M, E138A (n = 1) |
| N155H, E92Q, T97A (n = 1) | Q148H/R, G140S (n = 1) |
| N155H, V151I (n = 1) | |
| N155H, G163G/R (n = 2*) | |
| N155H, D232N (n = 1) | Y143R (n = 1) |

From: Hazuda, et al., 2007, 16th International HIV Drug Resistance Workshop, Barbados, Abstract #8

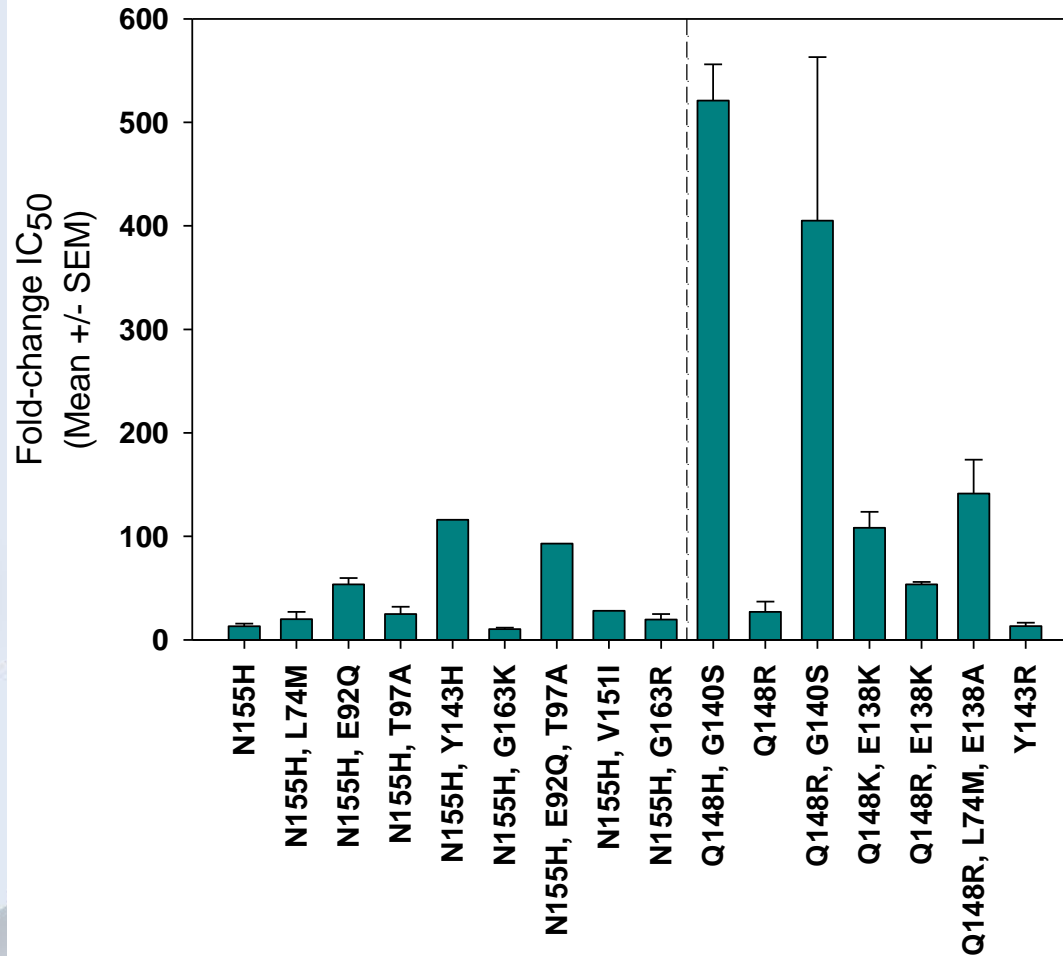
Phenotypic data for site-directed mutants: Signature mutations confer >10-fold raltegravir resistance



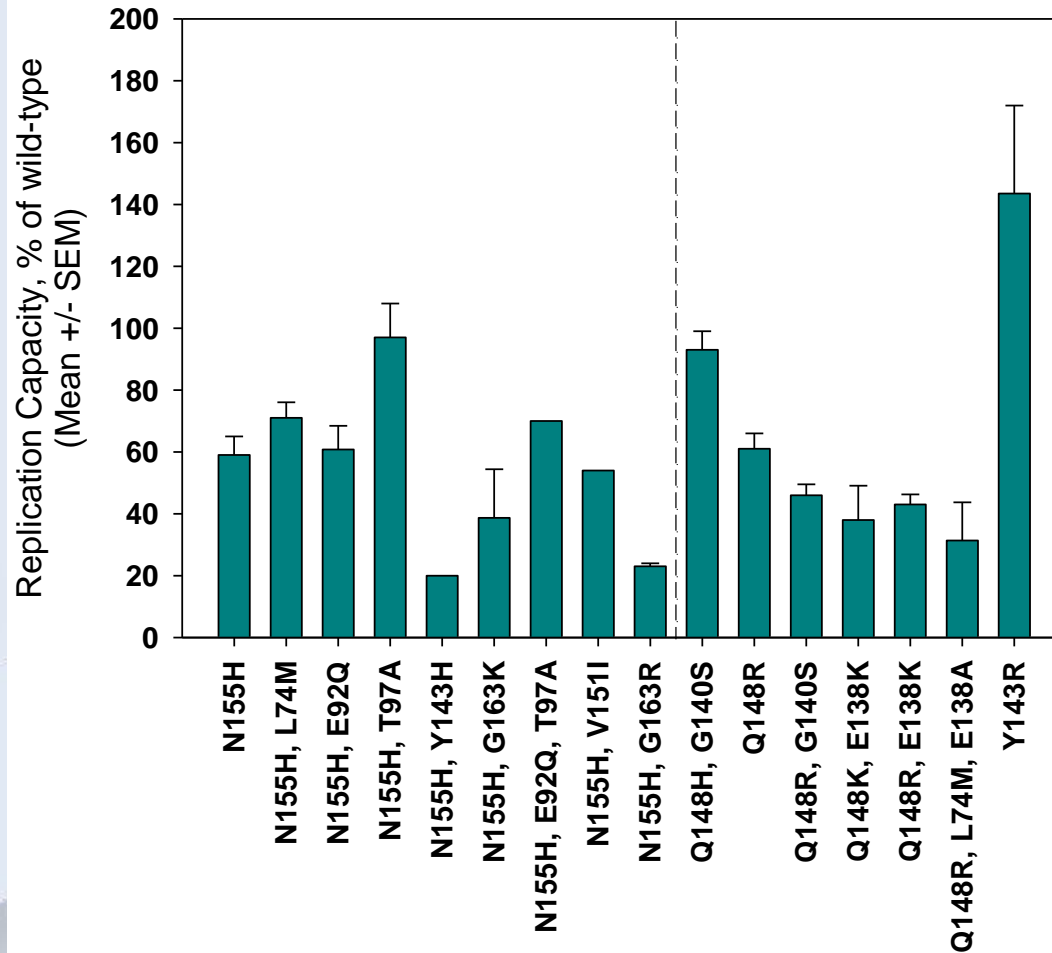
Replication capacity for site-directed mutants: Most signature mutations reduce viral replication capacity



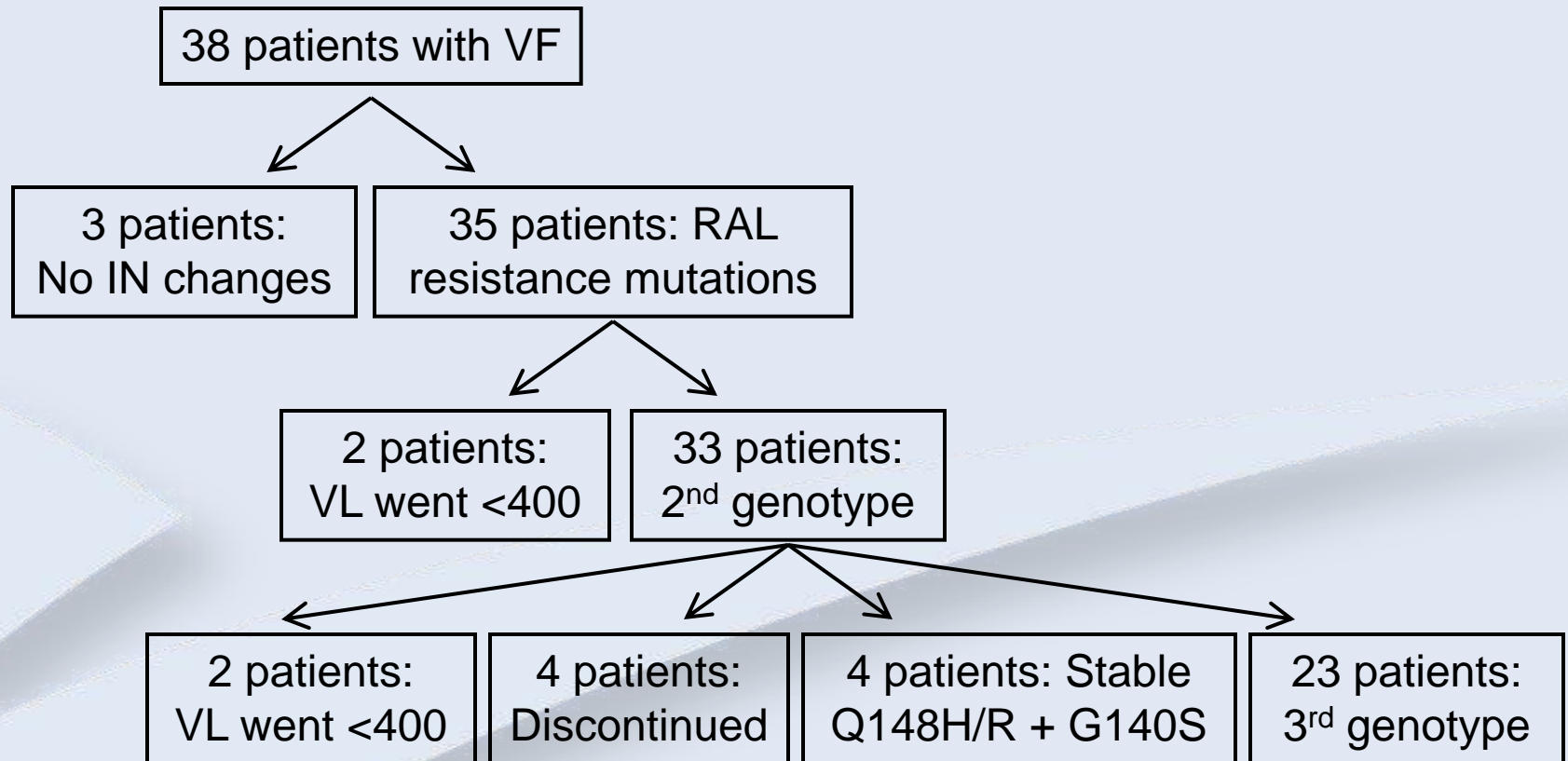
PN005 patterns: Secondary mutations augment raltegravir resistance when added to signature mutations



PN005 patterns: Secondary mutations variably affect viral replication capacity when added to signature mutations



PN005 longitudinal genotyping analysis (wk 48 virologic failures): Patient accounting



All PN005 integrase amino acid changes from baseline: Longitudinal genotype analysis

| Patient Number | Treatment Group | First Sign of Virologic Failure (Days) | Earliest Integrase Genotype | | Second Genotype | | Third Genotype | | OVERALL PATHWAY |
|----------------|-----------------|--|-----------------------------|--|----------------------|--------------------------------|----------------------|---|------------------------------------|
| | | | Plasma Sample (Days) | IN Changes from Baseline | Plasma Sample (Days) | IN Changes from Baseline | Plasma Sample (Days) | IN Changes from Baseline | |
| 1 | 400 | 112 | 112 | N155H | 131 | N155H | 196 | G140G/S, Q148Q/H, N155N/H ^{††} | SWITCHED: N155H --> Q148 |
| 2 | 400 | 112 | 112 | N155H | 167 | N155H, G163G/R | 420 | N155H, E92Q, E138K | 155 ONLY |
| 3 | 600 | 113 | 113 | N155H | 345 | N155H, T97T/A | 513 | N155H, L74L/M, T97A | 155 ONLY |
| 4 | 600 | 84 | 84 | N155H | 121 | Q148H, G140S | | Q148H, G140S | SWITCHED: N155H --> Q148 |
| 5 | 400 | 88 | 116 | N155H, E92Q | 176 | N155H, E92Q, T97A | 270 | N155N/H, E157E/Q, Y143H/Y, E92E/Q, T97A, D232N | 155 ONLY |
| 6 | 200 | 168 | 168 | N155H, G163G/R | 224 | N155H, G163G/R | 281 | Q148H, G140S | SWITCHED: N155H --> Q148 |
| 7 | 200 | 99 | 99 | N155H, G163R, D232N | 226 | Q148H, G140S | | G148H, G140S, T97T/A | SWITCHED: N155H --> Q148 |
| 8 | 400 | 170 | 170 | N155H, L74L/M | 282 | N155H, L74M, T97T/A | | Not Done (VL returned to <400) | 155 ONLY |
| 9 | 600 | 113 | 121 | N155H, T97A | 191 | Y143R, T97A | 239 | Y143R, T97A | SWITCHED: N155H --> Y143 |
| 10 | 200 | 231 | 295 | N155H, D232N | 450 | N155H, V151I, Y143Y/C | | Not Done (VL returned to <400) | 155 ONLY |
| 11 | 400 | 171 | 171 | N155H, V151I | | Not Done (VL returned to <400) | | Not Done (VL returned to <400) | 155 ONLY |
| 12 | 200 | 113 | 127 | N155N/H, T97T/A | 185 | Q148H, G140S | 437 | Q148H, G140S | SWITCHED: N155H --> Q148 |
| 13 | 200 | 174 | 174 | N155N/H, T97T/A | 236 | T97A | 502 | L74L/M, T97A, G163R | 155 ONLY |
| 14 | 400 | 57 | 57 | N155N/H, Q148K/Q/R [†] | 87 | N155H | 169 | Q148H, G140S | SWITCHED: MIX --> N155 --> Q148 |
| 15 | 400 | 57 | 57 | N155N/H, Q148Q/H, G140G/S | 113 | Q148H, G140S | 407 | Q148H, G140S | SWITCHED: MIX --> Q148 |
| 16 | 400 | 64 | 93 | N155N/H, Q148Q/H/R, G140G/S | 122 | Q148H, G140S | 156 | Q148H, G140S | SWITCHED: MIX --> Q148 |
| 17 | 200 | 56 | 56 | N155N/H, Q148Q/K, G163E/K [‡] | 140 | N155H, V151V/I, G163K | | Not Done (DISCON) | SWITCHED: MIX --> 155 [†] |
| 18 | 200 | 31 | 31 | N155N/H, Q148Q/R | 86 | Q148H, G140S | 366 | Q148H, G140S | SWITCHED: MIX --> Q148 |
| 19 | 200 | 86 | 86 | N155N/H, Q148Q/R, E138E/K | 113 | Q148H, G140S | 498 | Q148H, G140S | SWITCHED: MIX --> Q148 |
| 20 | 600 | 117 | 117 | N155N/H, Q148Q/R, E92E/Q ^{††} | 183 | N155H, E92Q, T97A | 348 | Q148H, G140S, E138K | SWITCHED: MIX --> 155 --> Q148 |
| 21 | 200 | 58 | 85 | NO CHANGE | | Not Done (DISCON) | | Not Done (DISCON) | NO CHANGE |
| 22 | 600 | 113 | 113 | NO CHANGE | | Not Done (DISCON) | | Not Done (DISCON) | NO CHANGE |
| 23 | 600 | 32 | 150 | NO CHANGE | | Not Done (DISCON) | | Not Done (DISCON) | NO CHANGE |
| 24 | 400 | 91 | 91 | Q148H, G140S | 134 | Q148H, G140S | | Not Done (stable 148/140) | 148 ONLY |
| 25 | 600 | 84 | 119 | Q148H, G140S | 561 | Q148H, G140S | | Not Done (stable 148/140) | 148 ONLY |
| 26 | 200 | 58 | 119 | Q148H, G140S | 279 | Q148H, G140S | | Not Done (DISCON) | 148 ONLY |
| 27 | 200 | 170 | 170 | Q148H, G140S | 240 | Q148H, G140S | | Not Done (DISCON) | 148 ONLY |
| 28 | 400 | 162 | 171 | Q148H, G140S | 361 | Q148H, G140S | | Not Done (DISCON) | 148 ONLY |
| 29 | 600 | 32 | 60 | Q148H, G140S | 228 | Q148H, G140S | 513 | Q148H, G140S | 148 ONLY |
| 30 | 600 | 126 | 126 | Q148K, E138K | 266 | Q148K, G140A, E138K | 507 | Q148K, G140A, E138K | 148 ONLY |
| 31 | 400 | 56 | 56 | Q148R, E138E/K | 115 | Q148R, E138E/K | 549 | Q148R, E138K, S147G | 148 ONLY |
| 32 | 600 | 167 | 167 | Q148R, G140G/S | 224 | Q148H/R, G140S | 436 | Q148H, G140S | 148 ONLY |
| 33 | 600 | 85 | 113 | Q148R | 246 | Q148H, G140S | 512 | Q148H, G140S | 148 ONLY |
| 34 | 400 | 249 | 249 | Q148R, G140S | 487 | Q148H, G140S | | Not Done (stable 148/140) | 148 ONLY |
| 35 | 600 | 57 | 57 | Q148R, G140S | 127 | Q148R, G140S | | Not Done (stable 148/140) | 148 ONLY |
| 36 | 400 | 90 | 112 | Q148R, L74L/M, E138A | | Not Done (VL returned to <400) | | Not Done (VL returned to <400) | 148 ONLY |
| 37 | 400 | 226 | 226 | V151V/I | 247 | N155H, Y143H | 401 | Q148H, G140S | SWITCHED: N155H/Y143 --> Q148 |
| 38 | 200 | 166 | 166 | Y143R | 286 | Q148H, G140S | 351 | Q148H, G140S | SWITCHED: Y143 --> Q148 |

Treatment group indicates the dose of RAL in mg (bid). First sign of viral rebound indicates the time point at which the viral load exceeded 400/ml. Data in bold type represent the "original genotype determinations".

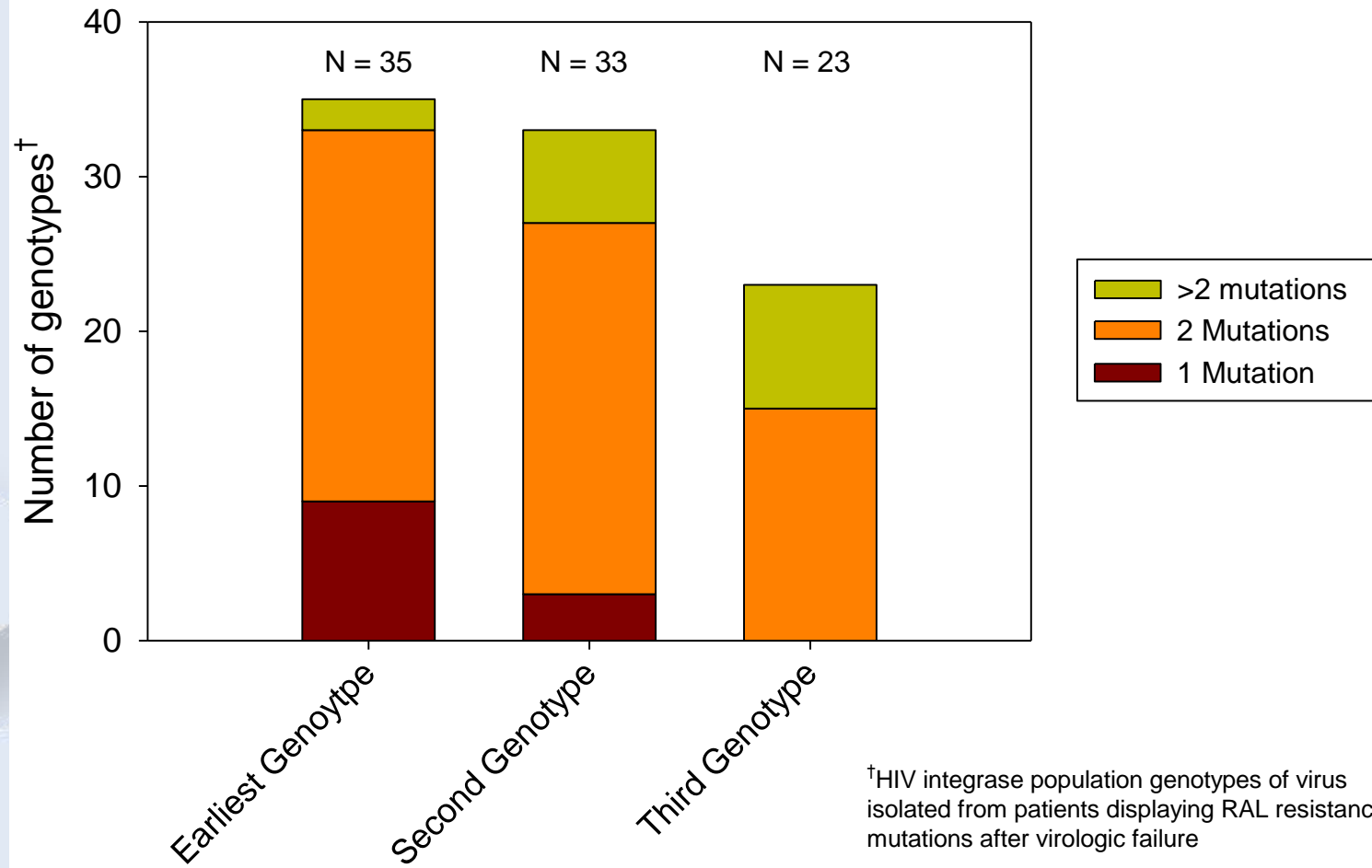
Shading indicates number of mutations: Blue = 1 mutation; Yellow = 2 mutations; Pink > 2 mutations. Each mixture was counted as a mutation except in where the population sequence showed a mixture of N155N/H

+ Q148Q/X, which was counted as 1 mutation because they are likely present on different viral genomes. Boxed genotypes were counted as "mixed/other".

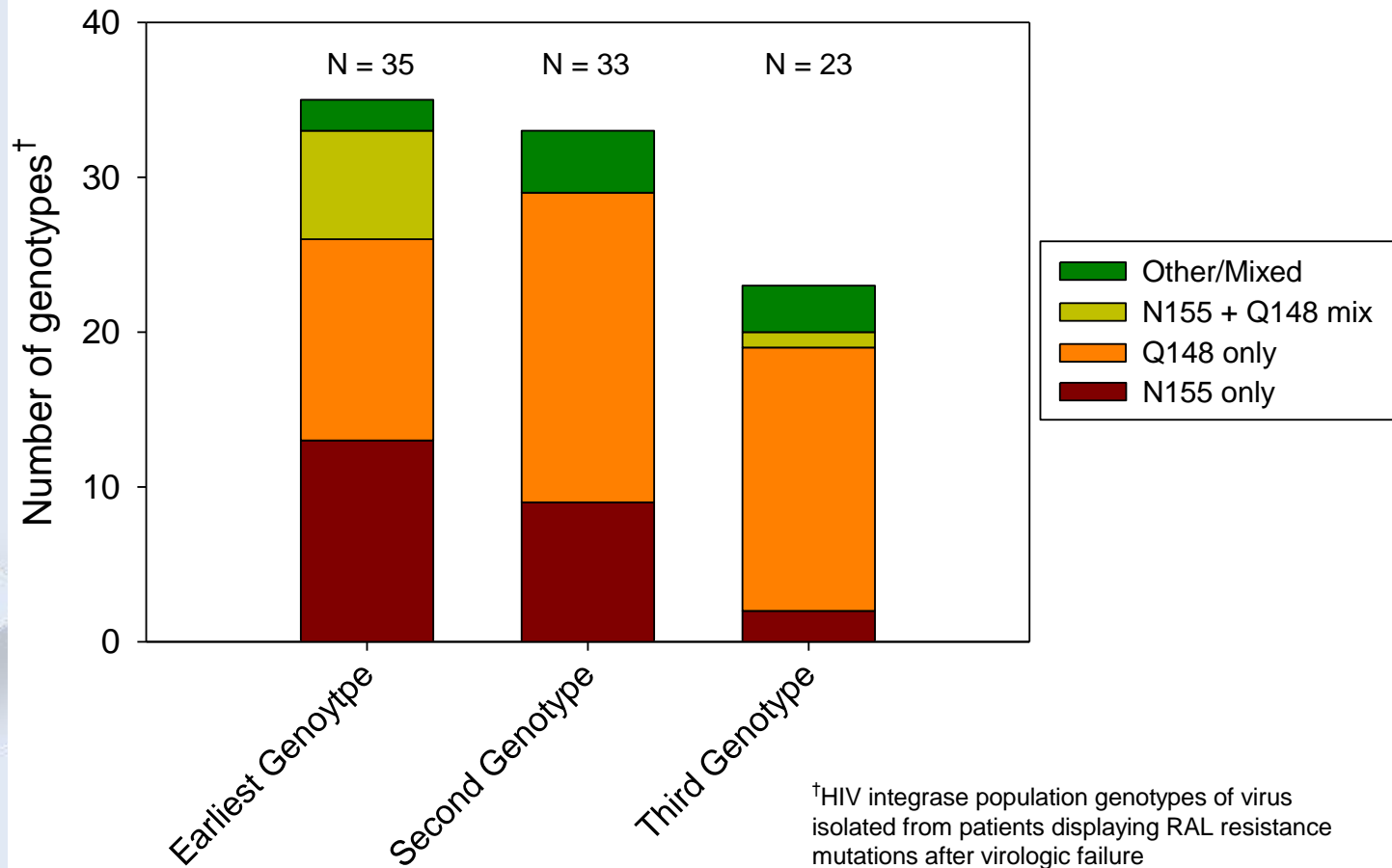
[†]Q148K/Q/R in one of four PCR products; N155N/H in 3 of 3 PCR products

[‡]Q148Q/K in 1 of 3 PCR products; N155N/H in 3 of 3 PCR products

Clinical raltegravir resistance mutations accumulate over time (PN005)



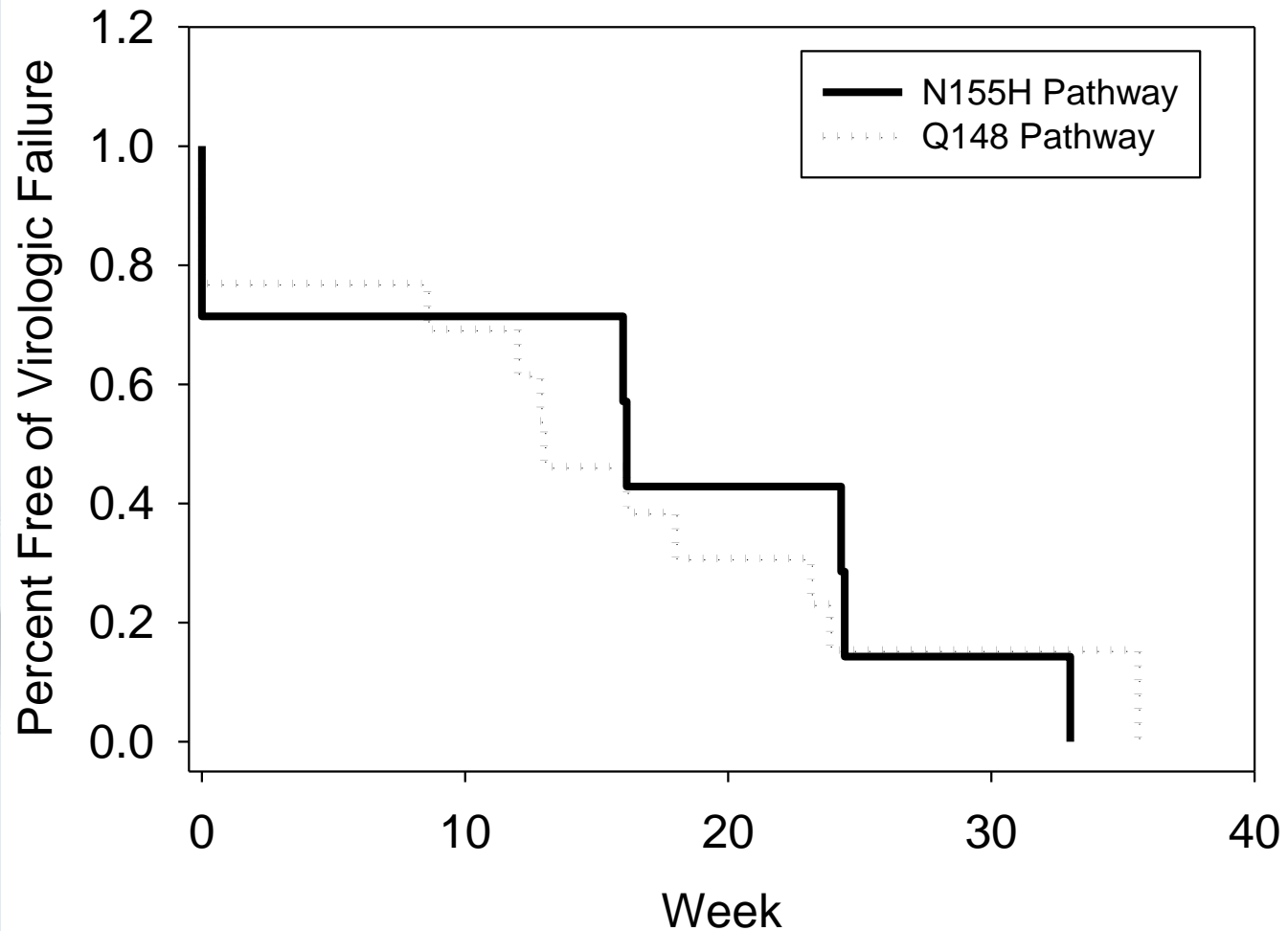
Clinical raltegravir resistance pathway evolution over time (PN005)



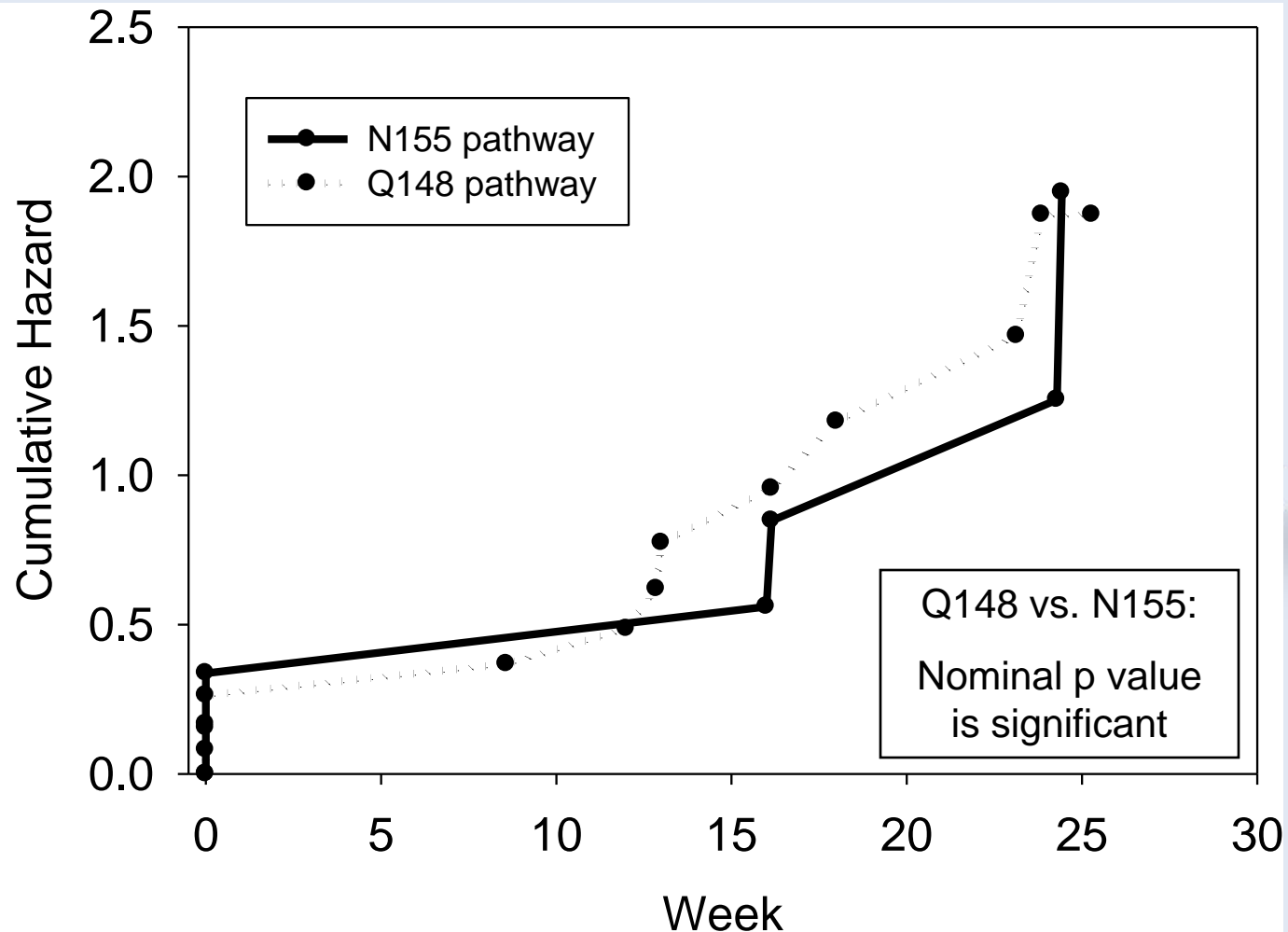
7 patients: virus evolved from N155N/H + Q148Q/X mix to pure Q148 pathway

5 patients: virus evolved from N155H pathway (no 148) to Q148 pathway

TLOVR for N155-only pathway vs. Q148-only pathway



Cumulative hazard for N155-only pathway vs. Q148-only pathway



Conclusions from PN005 longitudinal genotyping analysis

- ◆ **The integrase genotype can evolve over time**
 - Evidence of selective pressure on viruses with 1 mutation
 - Single mutations do not persist
 - “Stable” isolates have ≥ 2 mutations, generally with Q148 as the primary
- ◆ **Viruses with Q148 mutations are fitter than those with N155H**
 - Q148 mutations (\pm secondary mutations) have greater RAL resistance
 - In 7 patients, virus evolved from N155N/H + Q148Q/X mix to pure Q148 pathway
 - Time to loss of virologic response is longer for patients whose viruses evolve N155H but not Q148 mutations – NEED TO CONFIRM WITH LARGER DATA SET (e.g., PN018/019)
- ◆ **Though replication capacity may play a role in the competitive advantage of Q148 mutants, the advantage is best explained by higher-level resistance**

Acknowledgements: Protocol 005

All patients in Protocol 005

Investigators

| | | | |
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