



NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Resistance to Integrase Strand Transfer Inhibitors

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Raltegravir Resistance

Virologic Failure on Raltegravir

- A patient on tenofovir-emtricitabine (*Truvada*) and Raltegravir (*Isentress*) develops virologic failure with an HIV RNA level of 1,644 copies/ml 18 months after starting this regimen. A baseline genotype showed no mutations and 4 months prior he had an undetectable HIV RNA.
- **What type of resistance test should you order?**

Commercial Integrase Resistance Testing

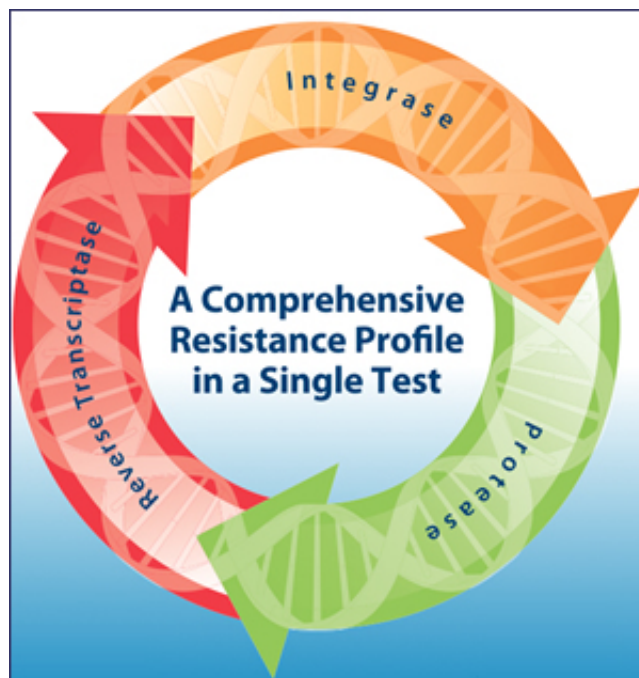
- Integrase **Genotype**
 - Quest Diagnostics
 - Lab Corp (Monogram Biosciences)
 - Virco Lab
- Integrase **Phenotype**
 - Lab Corp (Monogram Biosciences)
 - Virco



HIV Genotypic Resistance Testing that Includes Integrase

LabCorp (Monogram Biosciences)

GenoSurePRIme™
HIV DRUG RESISTANCE ASSAY PR RT IN



List Price \$890 (as of October 30, 2012)

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- **Genotype Result**

RT: **M184V**

Integrase: **N155H**

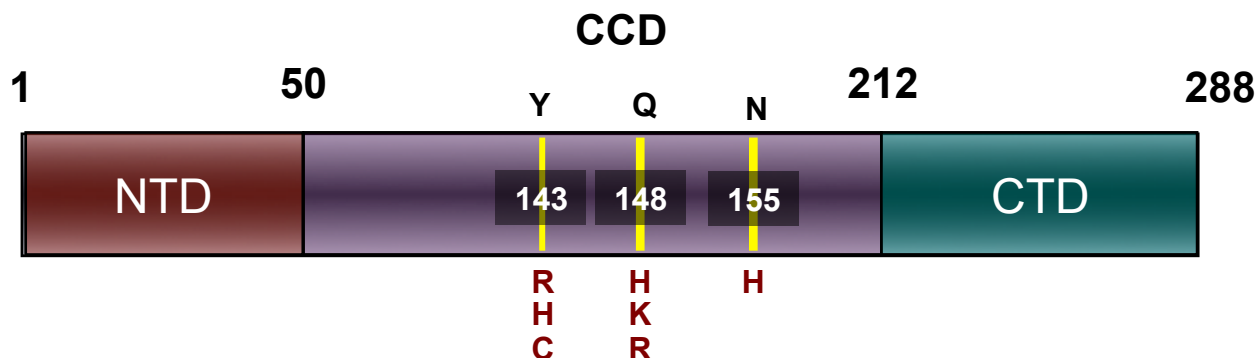
Protease: **No mutations**

Genotypic Resistance to Raltegravir

- **Primary Mutations**

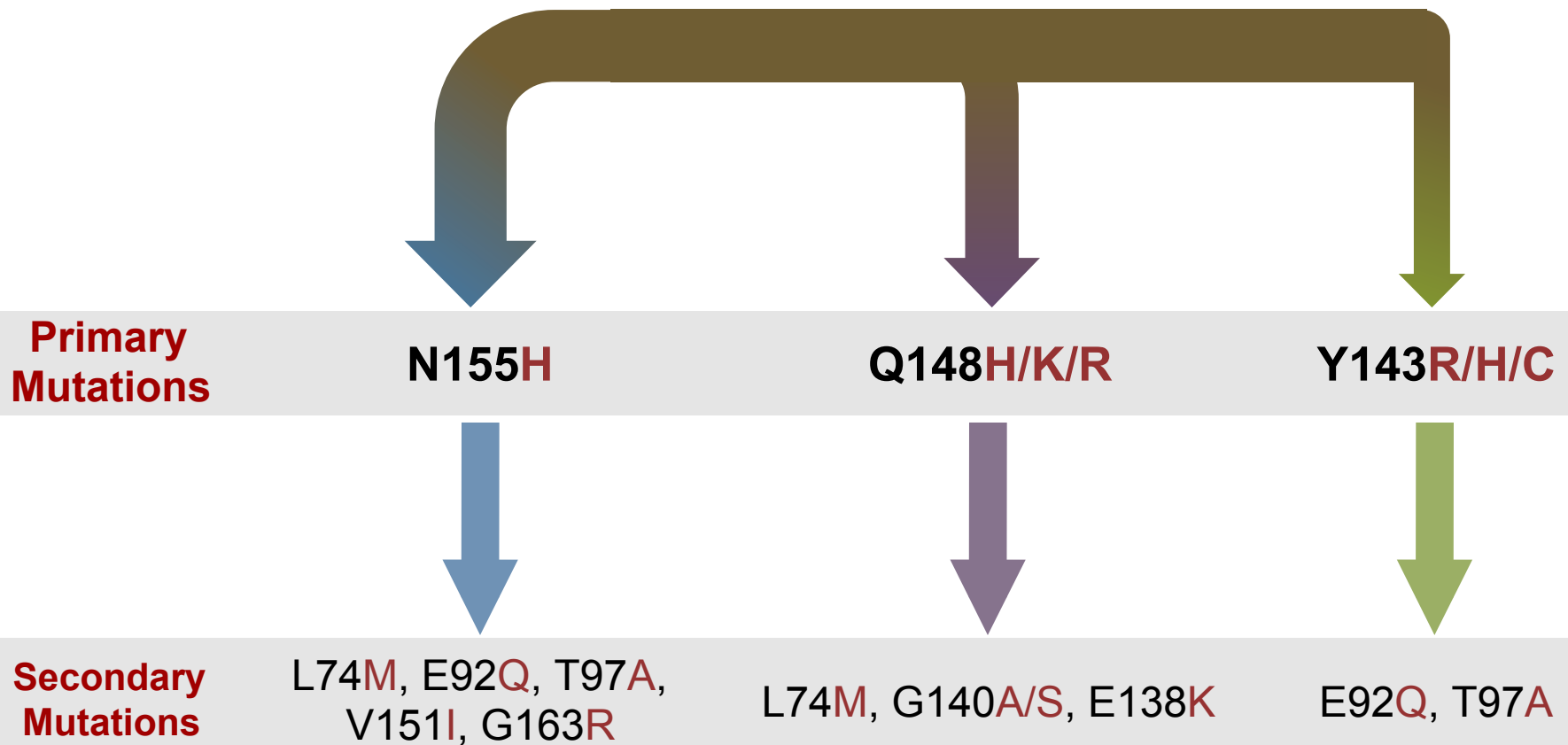
- N155H
- Q148H/K/R
- Y143R/H/C

Genotype: Primary Mutations

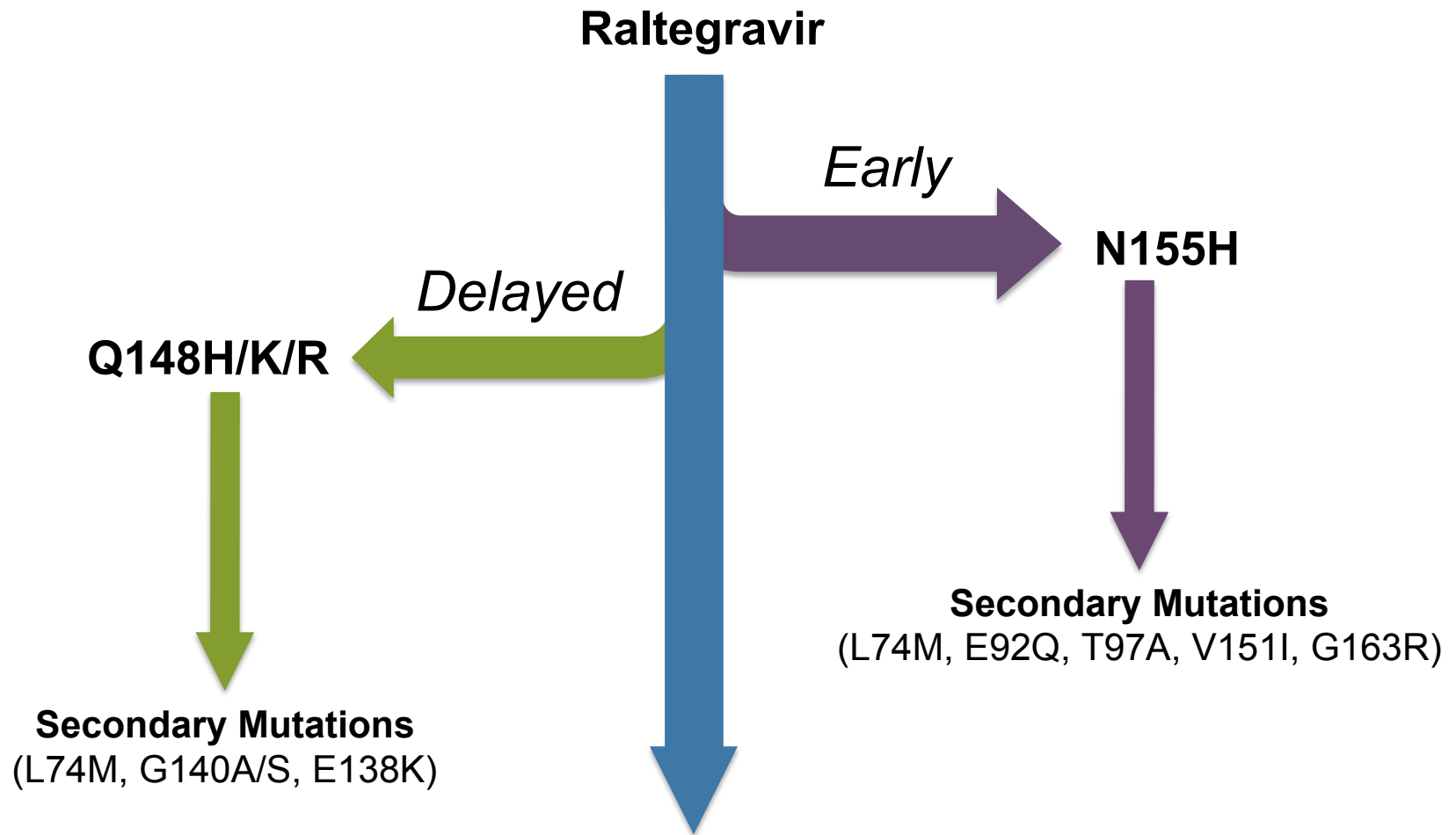


Major Pathways of Resistance with Raltegravir

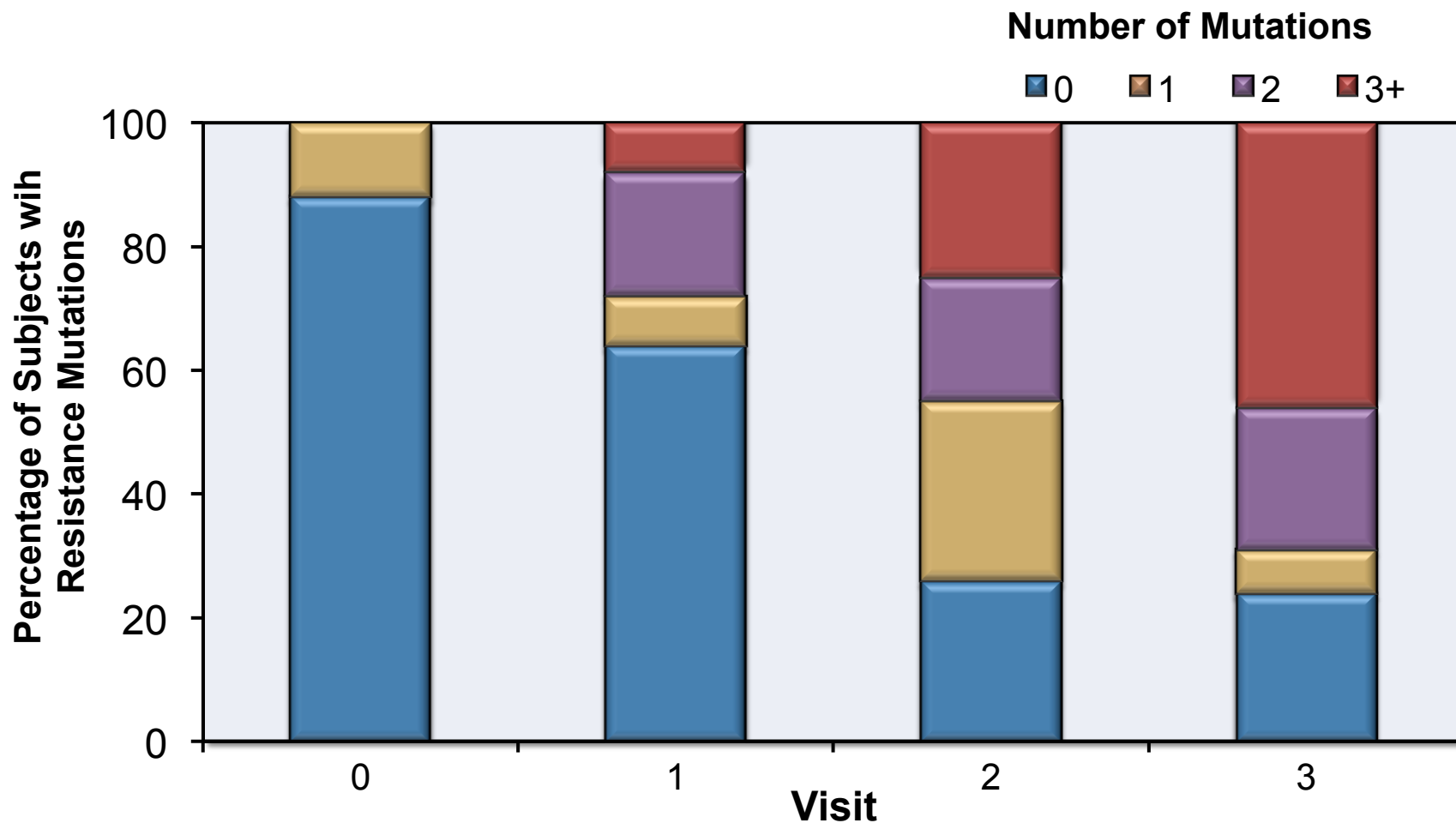
Raltegravir Resistance Pathways



Major Pathways of Resistance with Raltegravir



Evolution of Integrase Resistance During INSTI Failure SCOPE Study



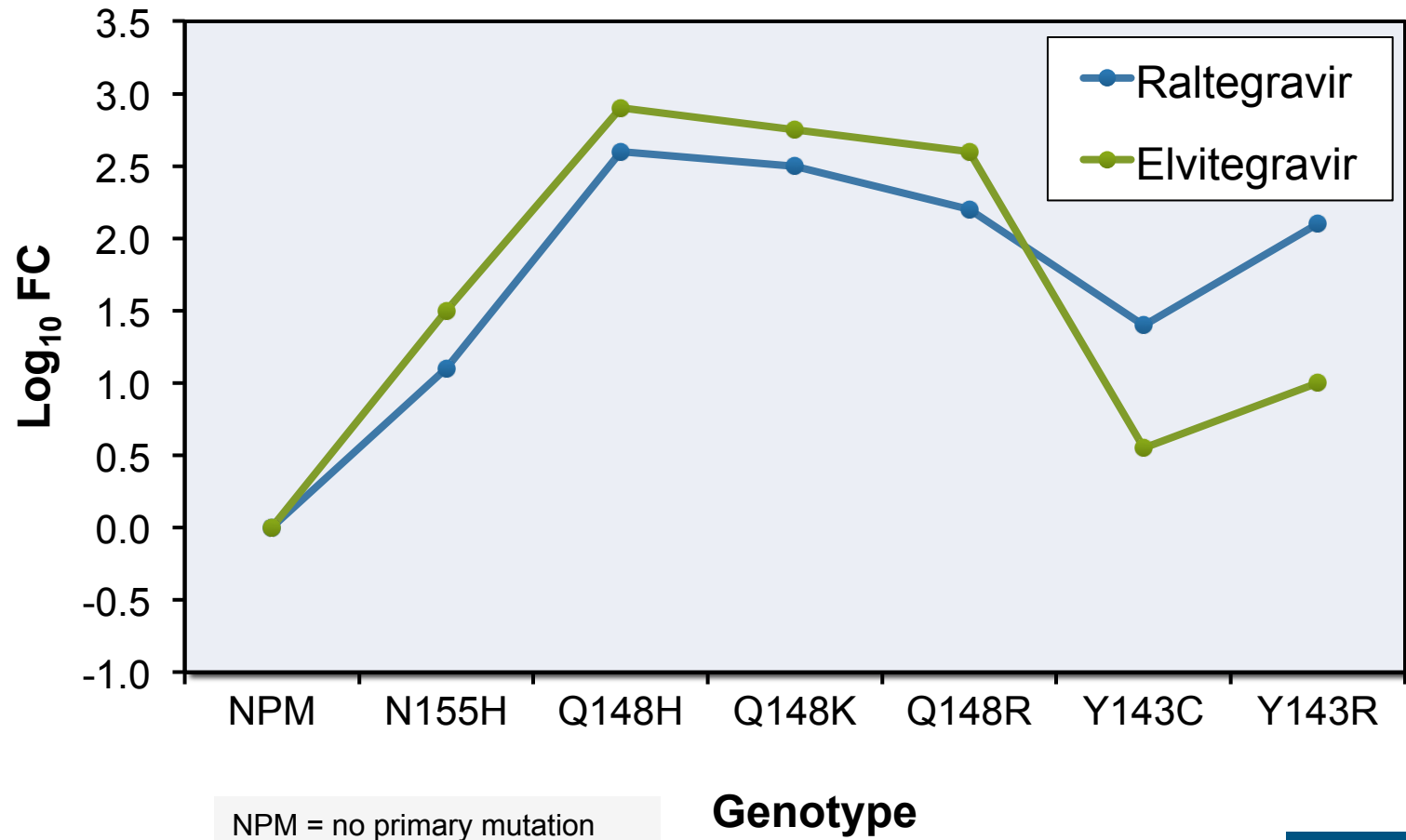


Virologic Failure on Raltegravir

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- **Genotype Result**
RT: **M184V**
Integrase: **N155H**
Protease: **No mutations**
- **Do you think the patient would respond to Elvitegravir?**

Raltegravir and Elvitegravir: Cross Resistance

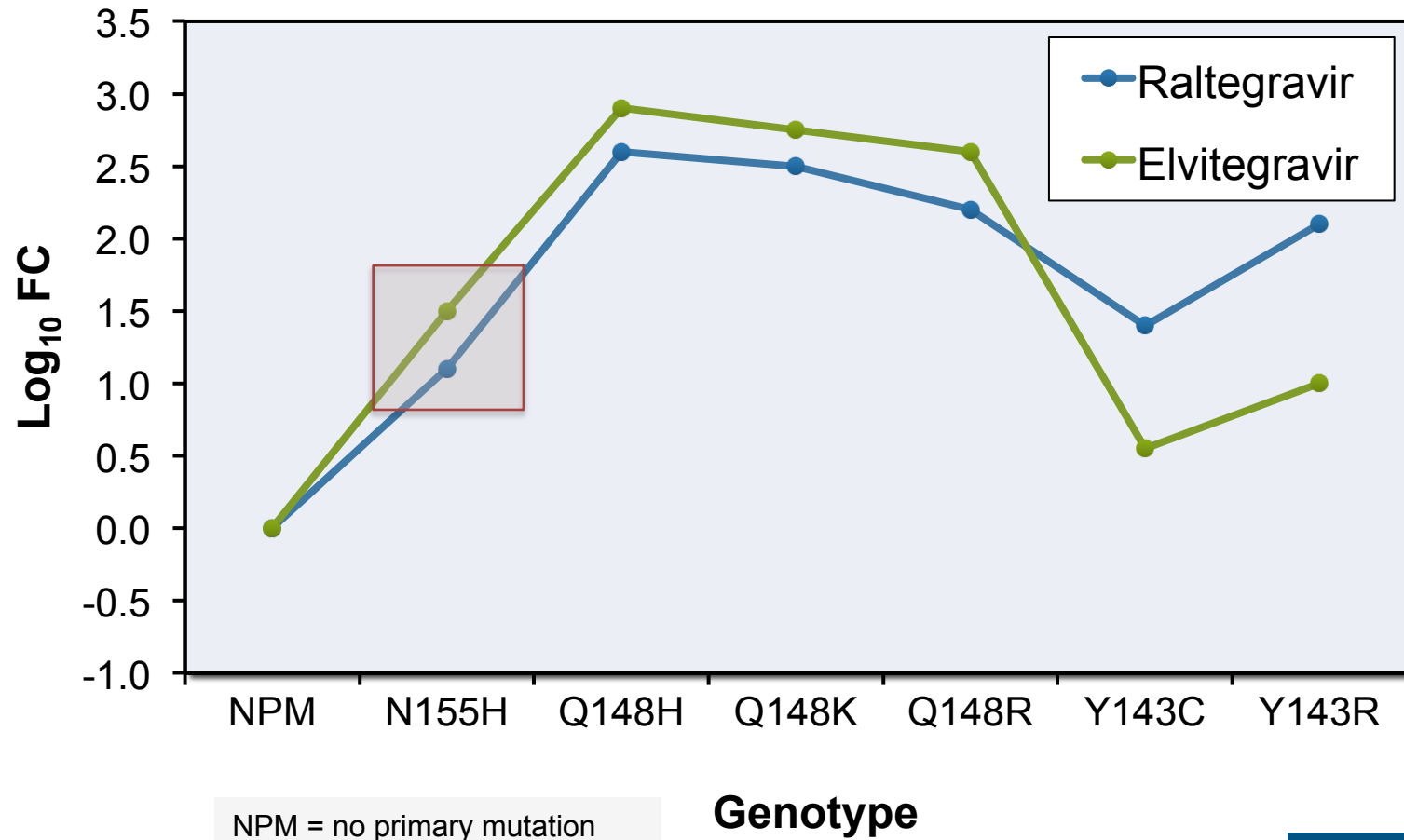
Graphical Representation of Mean log₁₀ Fold Change Values for Different Genotype



Source: Van Wesenbeeck L, et al. Antimicrob Agents Chemother. 2011;55:321-5.

Raltegravir and Elvitegravir: Cross Resistance

Graphical Representation of Mean log₁₀ Fold Change Values for Different Genotype



ANRS 138-Easier Trial

Low Level Viremia and Raltegravir Resistance

- **Background**

- Analysis of INSTI resistance in 49 patients with HIV RNA 50–500 copies/ml after switch from enfuvirtide to raltegravir

- **Results**

- Significant INSTI resistance mutations in 8%
- N155H in two and P145S in one
- Mutations not present on baseline proviral DNA analysis

- **Conclusion**

- INSTI resistance mutations can emerge during episodes of low level viremia in patients receiving raltegravir-containing regimens

Elvitegravir Resistance

Virologic Failure on Elvitegravir

- A patient on elvitegravir-cobicistat-tenofovir-emtricitabine (*Stribild*) develops virologic failure with an HIV RNA level of 3,288 copies/ml 9 months after starting this regimen? A genotype (including integrase) is performed and resistance is identified.
- **What resistance pattern would you expect to see?**
 - A. M184V, K103N
 - B. M184V, E92Q
 - C. K65R, N155H
 - D. K65R, K103N

Virologic Failure on Elvitegravir

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Resistance Data with EVG-Cobi-TDF-FTC Virologic Failures Data from Studies 102 and 103

Resistance Data from Studies 102 and 103	
Subjects with Virologic Failure (N =13)	
NRTI Resistance: Genotype Data	N = 12
A62A/V	2 (17%)
K65R	4 (33%)
M184V	12 (100%)
ISTI Resistance Genotype Data: 1° Mutations	N = 11
T66I	2 (18%)
E92Q	8 (73%)
Q148R	3 (27%)
N155H	3 (27%)

Resistance Data with EVG-Cobi-TDF-FTC Virologic Failures

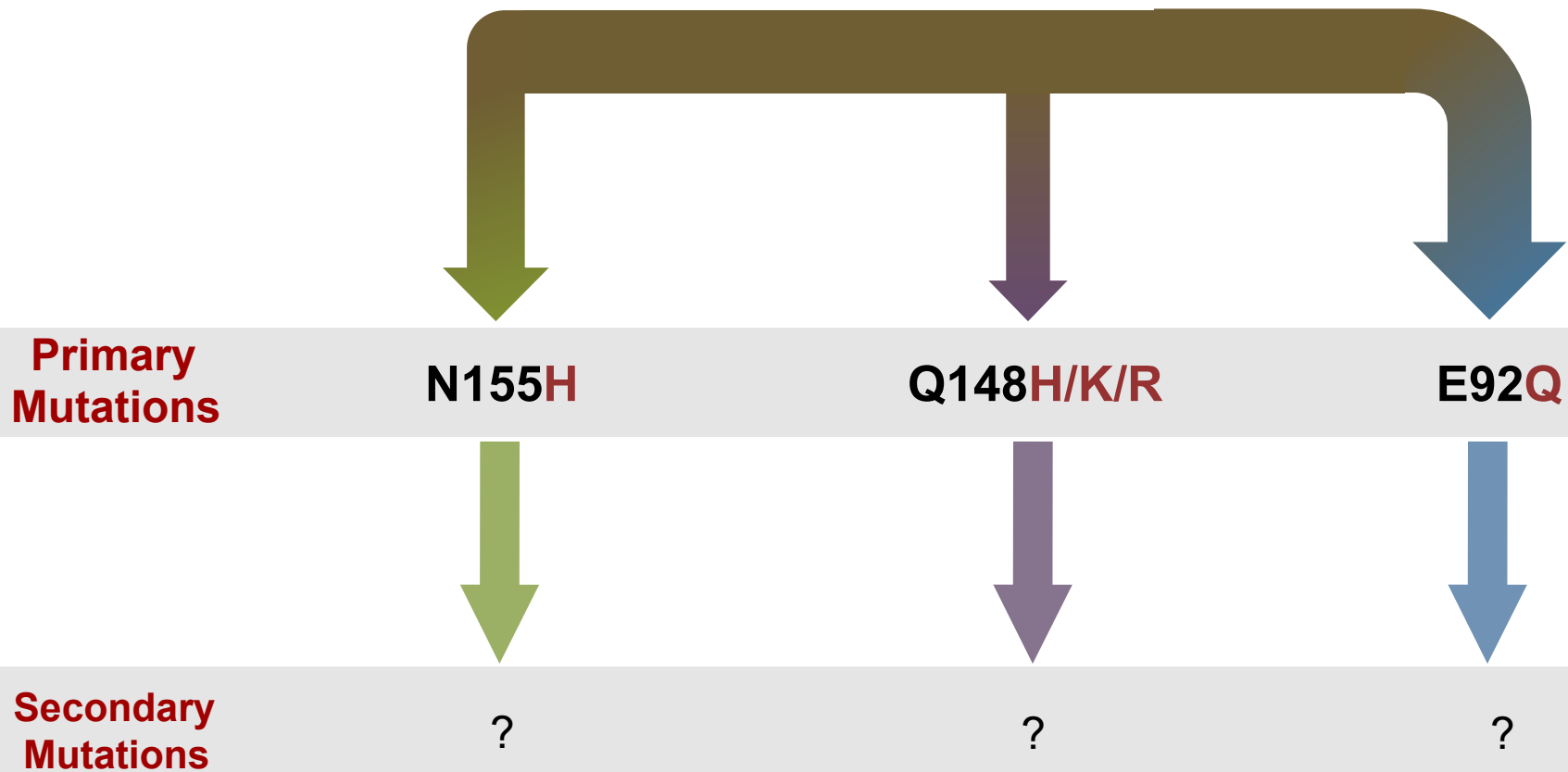
Genotypic Data from Studies 102 and 103

Patient	Genotype Data from Patients with Virologic Failure (N = 13)											
	NRTI			INSTI								
				Primary				Secondary				
1	A62V	K65R	M184V			Q148R				G140C		
2	A62V	K65R	M184V		E92Q			H51Y	L68V			
3		K65R	M184V		E92Q						S153A	
4	ND			T66A/I	E92Q		N155H					E157Q
5			M184V		E92Q	Q148R	N155H					
6			M184V		E92Q							
7			M184V		E92Q							
8			M184V				N155H					
9			M184I		E92Q							
10			M184V			Q148R						
11			M184V	T66I	E92Q							
12		K65R	M184V/I									
13			M184V									

Most common pattern of resistance: M184V and E92Q

Major Pathways of Resistance with Elvitegravir

Elvitegravir Resistance Pathways



Virologic Failure on Elvitegravir

- The genotype shows M184V and E92Q. You are going to change the patient's antiretroviral regimen.
- **Do you think the patient will likely respond to raltegravir?**
 - A. Yes
 - B. No

Resistance Data with EVG-Cobi-TDF-FTC Virologic Failures

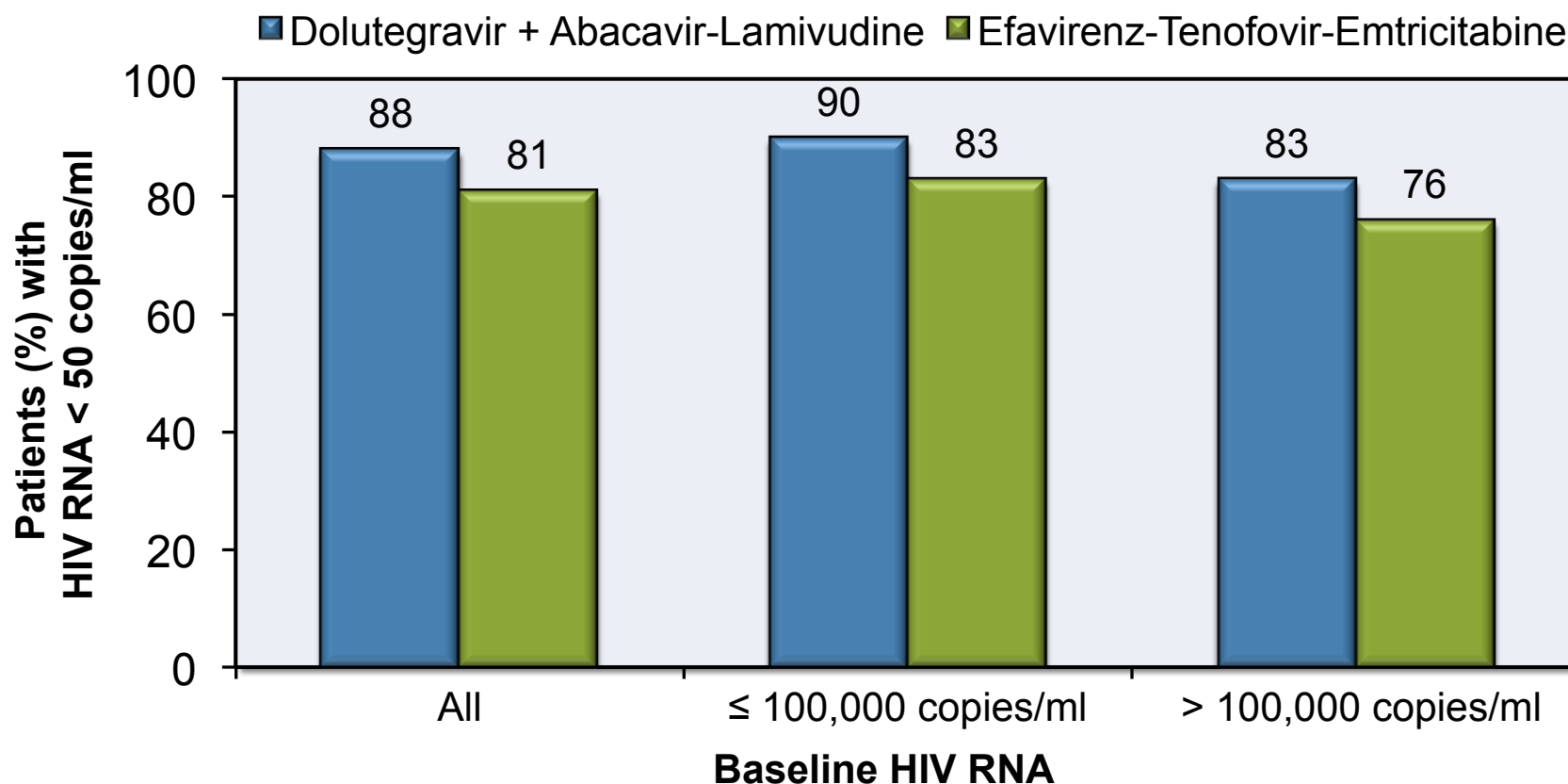
Phenotypic Data from Studies 102 and 103

Patient	Integrase Strand Transfer Inhibitor and Mean Fold Value Change	
	Elvitegravir (biologic cut-off = 2.5)	Raltegravir (biologic cut-off = 1.5)
1	>198	28
2	149	6.2
3	111	3.3
4	54	6.0
5	51	12
6	44	3.6
7	36	3.0
8	36	11
9	28	3.3
10	23	8.7
11	5.6	1.8

Dolutegravir

Dolutegravir-ABC-3TC versus Efavirenz-TDF-FTC

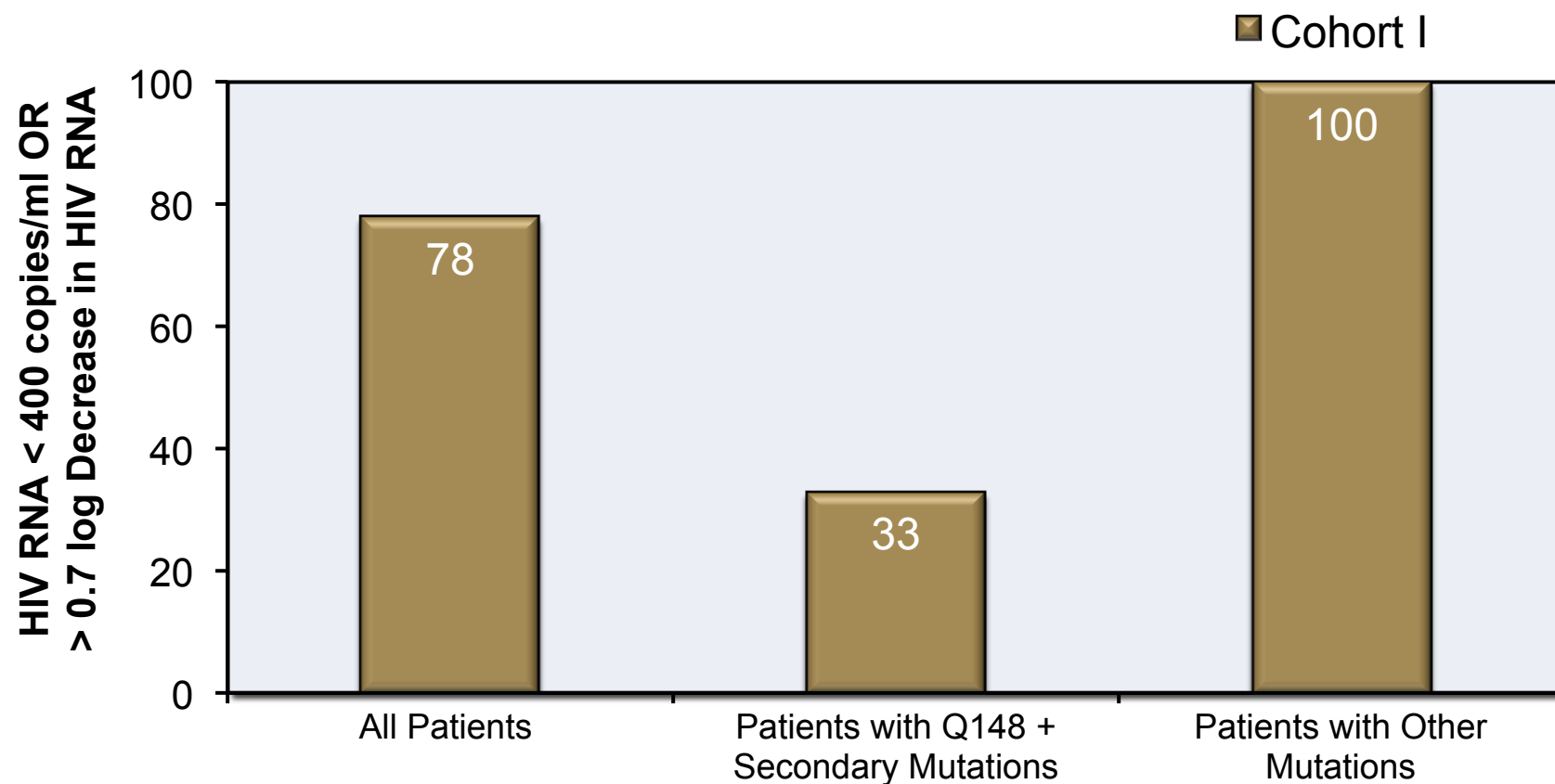
SINGLE: 48 Week Virologic Result



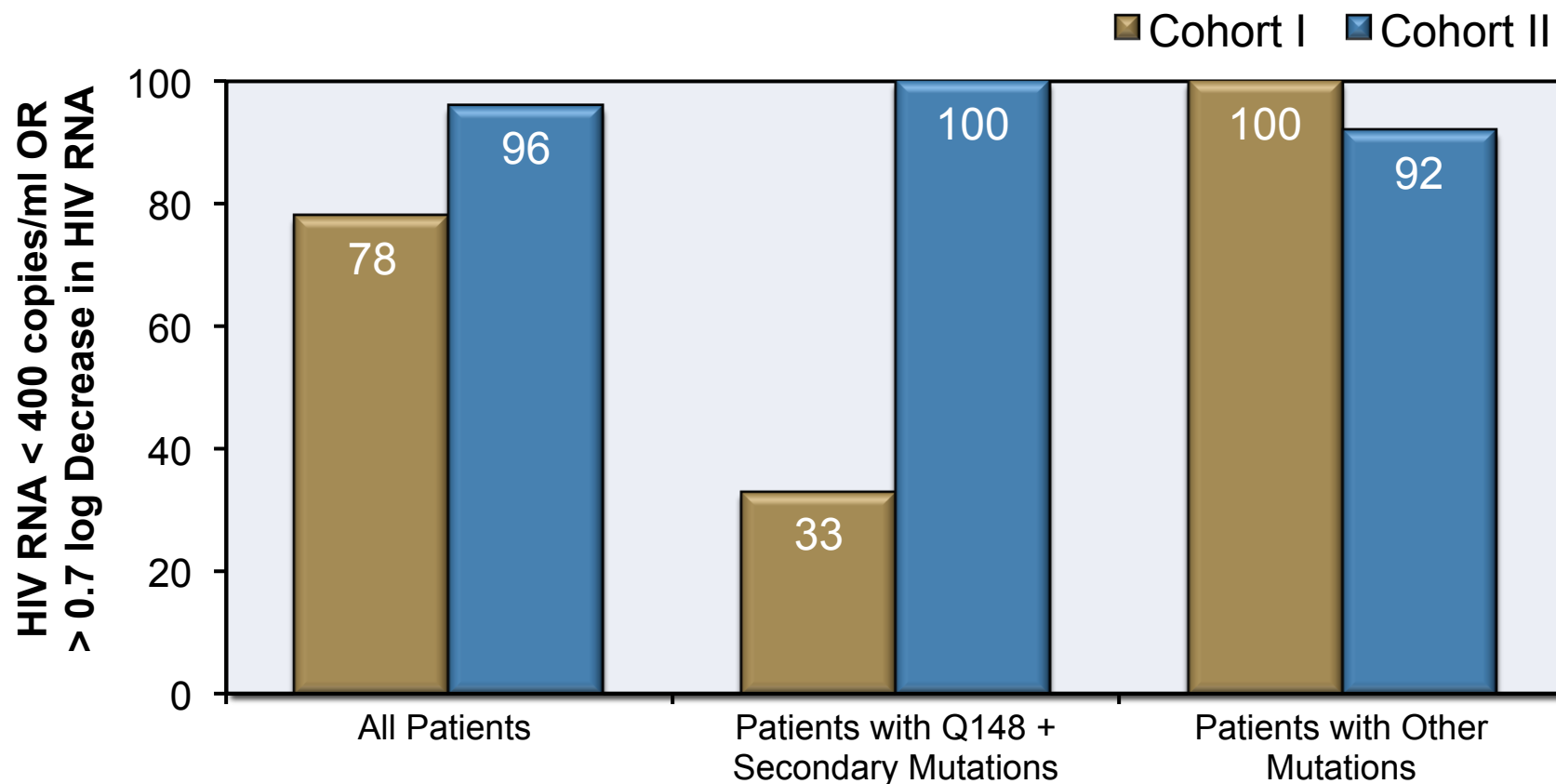
Dolutegravir-ABC-3TC: No Integrase Resistance with Virologic Failure

Dolutegravir (“572”) in Patients with Raltegravir Resistance

VIKING Cohort I: Results



Dolutegravir (“572”) in Patients with Raltegravir Resistance VIKING Cohort I and II: Results



INSTI-Resistance Associated Mutations

Major (Black) and High-Level Major (Red) Mutations

	T	E	G	S	Q	N	
Elvitegravir	66	92	140	147	148	155	IN
	I A K	Q	S A	G	H R K	H	

	T	E	G	Y	Q	N	
Raltegravir	66	92	140	143	148	155	IN
	A	Q	S A	R C H	H R K	H	

	E	G	Q	N	
Dolutegravir	92	140	148	155	IN
	Q	S A	H R K		

Resistance to Integrase Strand Transfer Inhibitors (ISTIs)

Key Concepts

- Raltegravir & elvitegravir have low-medium genetic barrier to resistance
- Dolutegravir has medium-high genetic barrier to resistance
- Genotype is appropriate test to evaluate resistance to ISTIs
- Raltegravir & elvitegravir have major cross-resistance
- Dolutegravir likely effective in early virologic failure with ISTI (RAL or EVG)
- Avoid prolonged failure with raltegravir or elvitegravir
- Dolutegravir requires higher dose when used with prior ISTI failure