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# Pre-Existing HIV-1 Integrase Polymorphisms do not Impact Treatment Response to Elvitegravir-Containing Fixed-Dose Combination Regimens in Treatment-Naive Patients

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## Introduction

- Integrase strand transfer inhibitors (INSTIs), including raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG), are a class of approved antiretroviral (ARV) drugs for the treatment of HIV-1 infection
- INSTI-based regimens are now recommended first-line regimens by all major treatment guidelines and are available in fixed-dose combinations (EVG/E/C/COBI/CTC/F/TDF; Stribild<sup>®</sup>, E/C/F/TAF; Genvoia<sup>®</sup>, and DTG/ABC/3TC; Triumeq<sup>®</sup>)
- Resistance to INSTIs develops through the selection of specific amino acid substitutions at specific positions in HIV-1 integrase (IN), including primary (major) and secondary (minor) INSTI resistance-associated mutations (RAMs) (see Figure 1)
- Primary INSTI-RAMs have been rarely detected in INSTI-naïve patients<sup>1-3</sup>. Thus, pre-treatment IN genotyping is currently recommended only if INSTI transmitted drug resistance (TDR) is a concern<sup>4</sup>
- Some secondary INSTI-RAMs may pre-exist INSTI-based treatment as natural IN polymorphisms, while others develop more frequently on INSTI-based treatment in the presence and/or absence of primary INSTI-RAMs
- It is unclear if INSTI-naïve patients are predisposed by pre-existing IN polymorphisms to delayed virologic suppression or an increased risk of earlier virologic failure on INSTI-based therapy

## Objectives

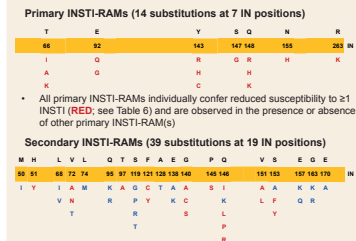
- To investigate the prevalence of pre-existing secondary INSTI-RAMs and evaluate their impact on INSTI susceptibility *in vitro* and treatment response in ARV treatment-naïve patients who enrolled on EVG-containing fixed-dose combination regimens

## Methods

- Integrase genotyping of pre-treatment (pre-Tx) plasma samples (screening or baseline) was performed prospectively or retrospectively across 14 Phase 2 or 3 Gilead clinical studies using the GeneSeq<sup>™</sup> or GenoSure<sup>™</sup> Integrase assay (Monogram Biosciences, South San Francisco, CA, USA)
  - Mixtures of mutant/wild-type amino acids were treated as full mutations across all 288 positions analyzed in HIV-1 IN
  - Frequency of IN variability (by position and amino acid substitution) was assessed and compared between patients harboring B and non-B subtype
- Treatment response (virologic success; VS, virologic failure; VF, no data; ND) across all 14 Phase 2 or 3 clinical studies at Week 48, 96, and 144 (HIV-1 RNA < 50 copies/mL) was calculated using U.S. FDA Snapshot algorithm using the full-analysis set (FAS) of enrolled patients and the FAS with pre-Tx IN genotype data
  - The impact of the presence of pre-treatment secondary INSTI-RAMs and IN polymorphisms on treatment response at Week 48, 96, and 144 was analyzed (Fisher's Exact test)
  - Statistical significance was assessed at P < 0.05 and P<sub>adj</sub> < 0.01/N
  - P<sub>adj</sub> controls for family-wise error rate by adjusting for multiple-hypothesis testing, where N = the number of comparisons<sup>5</sup>
- Integrase phenotyping of HIV-1 site-directed mutants (SDMs) was performed using the PhenoSense<sup>™</sup> Integrase assay (Monogram Biosciences, South San Francisco, CA, USA)

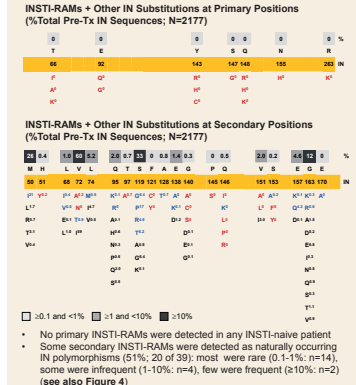
## Results

Figure 1. INSTI Resistance-Associated Mutations



- All primary INSTI-RAMs individually confer reduced susceptibility to ≥1 INSTI (RED; see Table 6) and are observed in the presence or absence of other primary INSTI-RAM(s)
- Most secondary INSTI-RAMs (22 of 39) individually maintain sensitivity to all INSTIs (BLUE; see also Table 1) and are observed in the presence or absence of primary INSTI-RAM(s)
- Some secondary INSTI-RAMs (17 of 39) individually confer reduced susceptibility to ≥1 INSTI (RED; see also Table 1) and are observed in the presence of primary INSTI-RAM(s)
- Secondary INSTI-RAMs may serve compensatory and/or accessory roles to further reduce INSTI susceptibility and/or improve HIV-1 replication fitness/capacity in the presence of primary INSTI-RAM(s)<sup>6,7</sup>

Figure 2. Frequency of Variation among Pre-Treatment IN Sequences (by Amino Acid Position and Substitution)



## Results (cont'd)

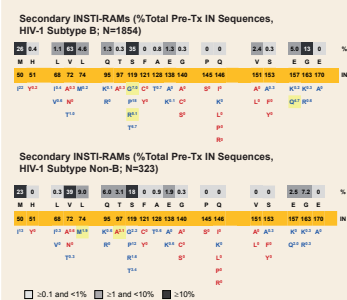
Table 1. INSTI Phenotypes of Mutant HIV-1 with Primary or Secondary INSTI-RAMs

PhenoSense™ IN assay (Monogram Biosciences). Phenotypic fold change (FC) EC<sub>50</sub> vs. NL4-3 wild-type virus above defined assay cutoffs for reduced susceptibility are colored. Replication capacity (RC) in the absence of drug shown as a percentage of NL4-3 wild-type virus.

SDM	FC EC <sub>50</sub> Relative to WT				RC, %WT
	EVG	RAL	DTG		
<b>Primary INSTI-RAMs</b>					
1 T66I	7.7	0.9	0.3	84	
2 T66A	7.5	0.9	0.3	69	
3 T66K	4.0	8.0	1.7	9	
4 E92Q	26	4.5	1.3	64	
5 E92Q	9.0	1.5	1.0	6	
6 Y143R	2.1	18.0	1.3	75	
7 Y143H	1.2	2.1	0.9	78	
8 Y143C	1.1	3.4	0.8	49	
9 S147G	4.1	1.1	1.0	108	
10 Q148R	92	25.0	1.1	70	
11 Q148H	4.9	15.0	0.4	54	
12 Q148K	94	37.0	1.5	36	
13 N155H	3.0	12.0	1.3	72	
14 R226K	4.6	1.1	1.7	111	

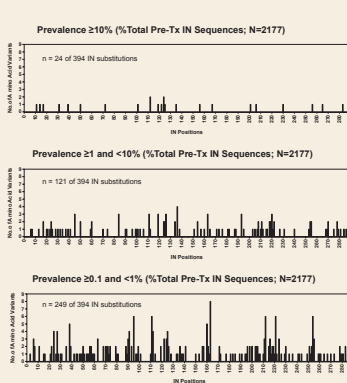
SDM	FC EC <sub>50</sub> Relative to WT				RC, %WT
	EVG	RAL	DTG		
<b>Secondary INSTI-RAMs</b>					
1 M50I	1.5	1.2	1.1	111	
2 H51Y	2.4	1.0	1.2	108	
3 L88I	1.9	0.9	0.7	78	
4 L88V	1.7	0.9	0.6	AF	
5 V122A	4.2	1.0	0.6	107	
6 V72N	6.1	1.1	0.8	75	
7 V72T	2.4	1.1	0.9	109	
8 L74M	1.7	1.2	0.7	93	
9 Q95K	1.9	1.3	1.1	47	
10 Q95R	1.7	1.2	1.0	30	
11 T97A	2.9	1.4	0.6	122	
12 S119G	1.5	1.1	0.9	156	
13 S119P	1.9	1.0	0.9	117	
14 S119R	2.1	1.3	1.1	66	
15 S119T	1.6	1.3	1.0	215	
16 F121C	AF	AF	AF	AF	
17 F121Y	16.0	5.3	0.6	6.3	
18 A128T	1.5	1.2	1.1	AF	
19 E138A	1.3	1.1	0.9	62	
20 E138K	1.4	0.8	0.9	97	
21 G140A	5.4	2.7	0.7	103	
22 G140C	6.1	1.1	0.5	28	
23 G140S	5.0	1.4	0.8	95	
24 P145S	28.0	0.7	0.3	39	
25 Q146I	21.5	3.2	2.2	80	
26 Q146K	2.2	0.9	0.8	86	
27 Q146L	15.0	1.0	1.3	67	
28 Q146P	6.5	0.8	0.5	111	
29 Q146R	4.9	1.6	1.4	80	
30 V151A	2.7	1.4	0.8	109	
31 V151L	20.0	15.0	1.6	6	
32 S153A	1.9	1.3	1.0	110	
33 S153F	2.7	1.2	1.9	89	
34 S153Y	3.0	1.2	2.1	81	
35 E157K	1.4	1.4	1.6	19	
36 E157Q	1.8	1.3	1.1	89	
37 G163K	1.5	1.2	0.9	74	
38 G163R	1.8	1.3	1.1	74	
39 E170A	1.6	1.2	1.0	71	

Figure 3. Frequency of Variation among Pre-Treatment IN Sequences by HIV-1 Subtype (B vs. Non-B)



- The distribution of IN genotypes was comparable between E/C/F/TDF and E/C/F/TAF treatment groups, with subtype B predominant in both groups (85% overall, 1854 of 2177 subjects)
- Prevalence of secondary INSTI-RAMs rarely differed by 22-fold between B and non-B subtypes (5 of 39 variants); none differed by ≥10-fold
- Some secondary INSTI-RAMs were more prevalent in subtype B (S119G/R, E157Q) or non-B (L74M, T97A), as highlighted in light yellow

Figure 4. Distribution of the Number of Amino Acid Substitutions by IN Position



- No primary INSTI-RAMs were detected in any INSTI-naïve patient
- Some secondary INSTI-RAMs were detected as naturally occurring IN polymorphisms (51%); 20 of 39; most were rare (0.1-1%; n=14), some were infrequent (1-10%; n=4), few were frequent (≥10%; n=2) (see also Figure 4)

Table 2. Integrated Virologic Outcome at Weeks 48, 96, and 144 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS w/ Pre-Tx IN Data)

Study	Subjects	Phase	Enroll Year	Treatment Arm	FAS w/ Pre-Tx IN Data	Week 48						Week 96						Week 144					
						VS (%)	VF (%)	ND (%)	TOTAL	VS (%)	VF (%)	ND (%)	TOTAL	VS (%)	VF (%)	ND (%)	TOTAL						
GS-US-236-0102	TN	Ph3	2012	E/C/F/TDF	318	277 (87%)	25 (8%)	16 (5%)	318	276 (87%)	25 (8%)	17 (5%)	318	254 (80%)	26 (8%)	38 (12%)	318						
GS-US-236-0104	TN	Ph2	2009	E/C/F/TDF	2	2 (100%)	0	0	2	NA	NA	NA	NA	NA	NA	NA	NA						
GS-US-236-0111	TN	Ph3	2013	E/C/F/TAF	2	1 (50%)	1 (50%)	0	2	1 (50%)	1 (50%)	0	2	NA	NA	NA	NA						
GS-US-236-0128	TN	Ph3	2012	E/C/F/TDF	25	19 (76%)	5 (20%)	1 (4%)	25	NA	NA	NA	NA	NA	NA	NA	NA						
GS-US-236-0102	TN	Ph2	2012	E/C/F/TDF	3	3 (100%)	0	0	3	NA	NA	NA	NA	NA	NA	NA	NA						
GS-US-236-0104	TN	Ph3	2013	E/C/F/TDF	430	399 (93%)	11 (3%)	20 (5%)	430	379 (88%)	11 (3%)	40 (9%)	430	NA	NA	NA	NA						
GS-US-236-0111	TN	Ph3	2013	E/C/F/TDF	435	386 (89%)	23 (5%)	26 (6%)	435	358 (82%)	24 (6%)	53 (12%)	435	NA	NA	NA	NA						
<b>Total</b>					<b>1582</b>	<b>1417 (89%)</b>	<b>60 (4%)</b>	<b>65 (4%)</b>	<b>1582</b>	<b>1363 (86%)</b>	<b>73 (5%)</b>	<b>148 (9%)</b>	<b>1582</b>	<b>1276 (81%)</b>	<b>41 (3%)</b>	<b>48 (3%)</b>	<b>385</b>						
GS-US-236-0102	TN	Ph2	2012	E/C/F/TAF	432	402 (93%)	13 (3%)	17 (4%)	432	385 (89%)	16 (4%)	31 (7%)	432	NA	NA	NA	NA						
GS-US-236-0104	TN	Ph3	2013	E/C/F/TAF	48	42 (88%)	3 (6%)	3 (6%)	48	NA	NA	NA	NA	NA	NA	NA	NA						
GS-US-236-0111	TN	Ph3	2013	E/C/F/TAF	431	396 (92%)	18 (4%)	17 (4%)	431	362 (84%)	23 (5%)	46 (11%)	431	NA	NA	NA	NA						
GS-US-236-0112	TN	Ph3	2013	E/C/F/TDF	0	0	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA						
GS-US-236-0128	TN	Ph3	2012	E/C/F/TDF	0	0	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA						
<b>Total</b>					<b>915</b>	<b>844 (92%)</b>	<b>38 (4%)</b>	<b>35 (4%)</b>	<b>915</b>	<b>747 (82%)</b>	<b>38 (4%)</b>	<b>77 (8%)</b>	<b>883</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>						
GS-US-236-0102	TN	Ph3	2012	E/C/F/TDF	2177	1961 (89%)	116 (5%)	100 (5%)	2177	1790 (82%)	115 (5%)	195 (9%)	2177	1704 (78%)	41 (2%)	48 (2%)	387						

Figure 5. Integrated Virologic Outcome at Weeks 48, 96, and 144 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL

