Mutations Associated with Reduced Susceptibility to INSTIs

Robert Shafer, MD
Professor of Medicine
Stanford University

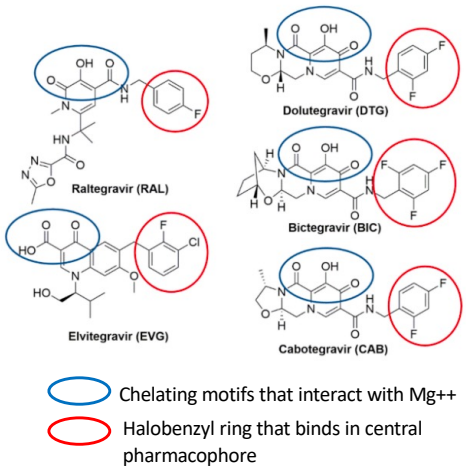
This talk is about mutations responsible for resistance to the integrase strand transfer inhibitors most commonly referred to as INSTIs.

Disclosures

- Gilead Sciences (2022): Advisory board and speaking honorarium.
- ViiV Healthcare (2022): Speaking honorarium.

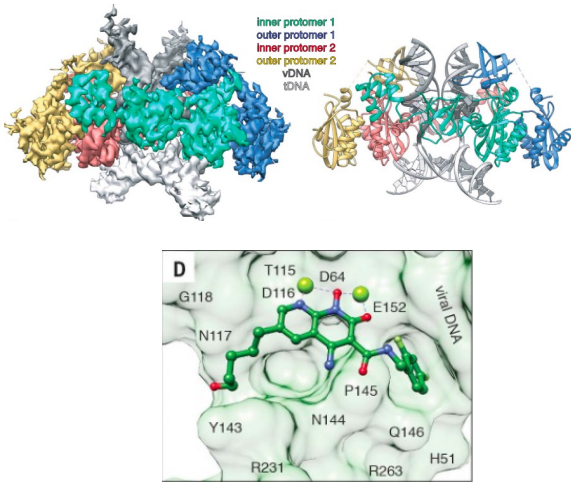
These are my disclosures.

INSTIs



Smith SJ. Integrase Strand Transfer Inhibitors Are Effective Anti-HIV Drugs. Viruses 2021

IN Tetramer Bound to Viral and Host DNA



Passos DO. Structural Basis for Strand-Transfer Inhibitor Binding to HIV Intasomes. Science 2020

1. Two chemical steps are required for integration: (i) 3'-end processing, in which IN cleaves two nucleotides from each 3'-end of viral DNA, and (ii) Strand transfer, in which IN inserts the ends of the viral DNA into target DNA.
2. The INSTIs block the strand transfer reaction and selectively interact with both the bound viral DNA and IN enzyme.
3. This figure shows the chemical structures of the FDA approved INSTIs.
4. The chelating motifs that interact with Mg2+ cofactors in the IN active site are highlighted with a blue circle. The halobenzyl moieties, which are connected to the centralized pharmacophore by a linker group, are circled in red.
5. The figure on the right shows the 3-D cryo-EM structure of the IN tetramer bound to viral and host chromosomal target DNA.
6. Each monomeric enzyme has 3 domains - a central catalytic domain that extends from position 51 to 212. It contains the active site and most of the INSTI-resistance mutations.
7. The N-terminal domain, positions 1-50, plays an important role in enzyme multimerization. The C-terminal domain is involved in DNA binding
8. This figure shows an investigational INSTI situated close to the active site residues D64, D116, and E152 and close to the two Mg co-factors.
9. Several DRMs are shown but because IN interacts with both viral DNA and host

Passos DO. Cryo-EM struc strand tran

DNA and because it is tetrameric, it is impossible to obtain a single view that shows most INSTI DRMs.

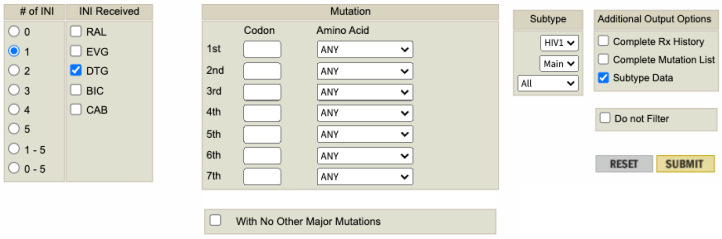
Outline

- Mutations selected by INSTIs
  - In vitro
  - In patients
- Effect of DRMs on INSTI susceptibility.
- Antiviral response to treatment with second-generation INSTIs.

1. This talk will review three types of data that inform our understanding of INSTI resistance.
2. The first is an analysis of which DRMs are selected in patients receiving each of the INSTIs
3. The second is an analysis of how DRMs affect the susceptibility of DRMs
4. The third is data on the response to treatment receiving 2nd-generation INSTIs.
5. The vast majority of the data are available for DTG and nearly all of the data comes from its use in INSTI-naïve persons.

Integrase Sequences or DRM Lists From INSTI-Treated Patients

Detailed Integrase Inhibitor/Mutation Query

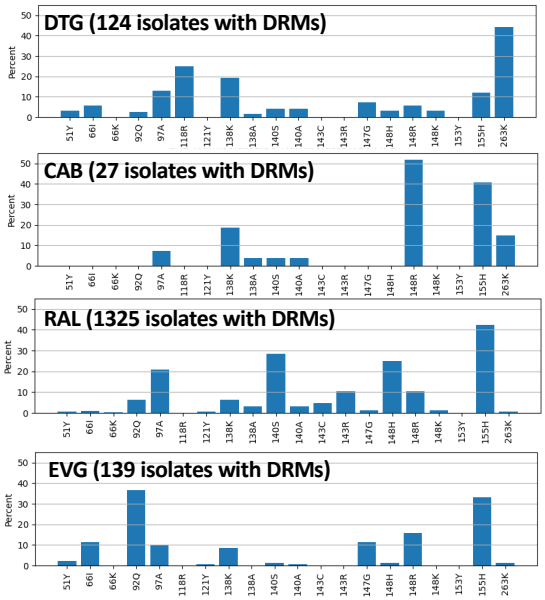


https://hivdb.stanford.edu/cgi-bin/InhibitorsMutations.cgi?Gene=IN

Available Sequences (or Mutation Lists)

Drug	FDA	# Pts
RAL	2007	2182
EVG	2012	330
DTG	2013	396
BIC	2018	1
CAB	2021	36

1. The Stanford HIVDB makes it possible to download IN sequences or lists of mutations from patients who were treated with different INSTIs.
2. For example, this form requests all isolates from persons who have received DTG as their only INSTI.
3. There are no requirements for specific mutations to be present.
4. The table at the right summarizes the number of available sequences or mutation lists available from persons who have received a single INSTI.
5. Ideally, we would like to have complete IN sequence from each patient. However, we often only have a list of mutations provided by authors, which may possibly be missing important mutations.
6. As you can see from the table, there are few data in HIVDB on the selection of DRMs for the two most recently approved INSTIs, BIC and CAB.
7. The lack of data for BIC is likely due to it being much rarely used in salvage therapy situations compared to DTG and the first-generation INSTIs and possibly because of its potentially higher barrier to emergent resistance. It is also primarily used in UIC settings where patients undergo frequent virological monitoring.

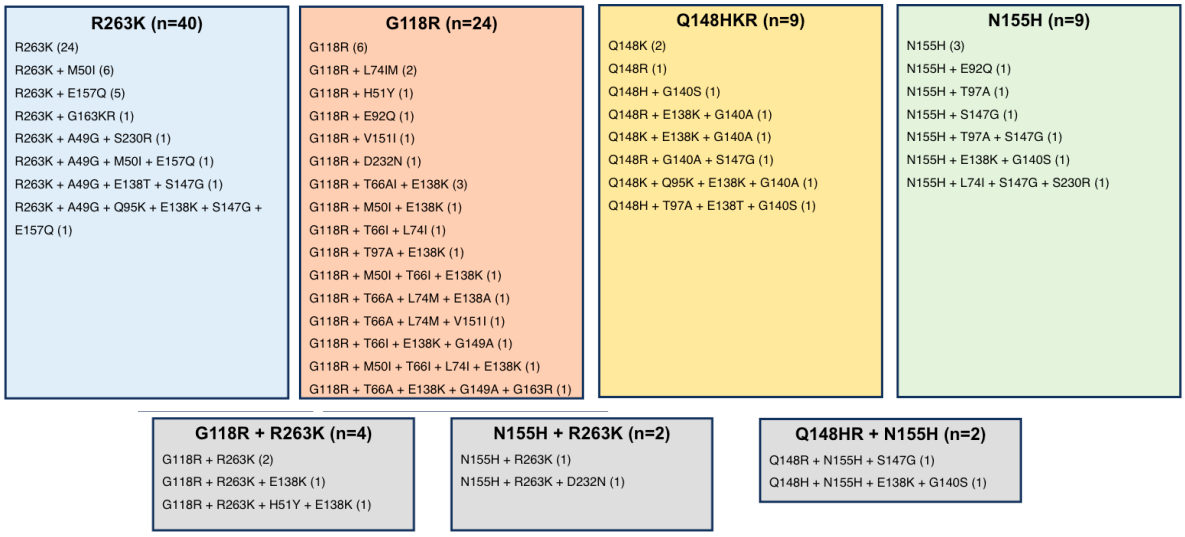


INSTI DRMs Selected in Patients

- DTG signature DRMs:
  - G118R, Q148HRK, N155H, R263K
- DTG accessory DRMs:
  - H51Y, T66I, E92Q, T97A, E138K, G140AS, S147G
- CAB similar signature mutations
  - Q148R most common; G118R and R263K uncommon.
  - G140R reported in one patient.

1. This slide summarizes the mutations observed in patients receiving DTG, CAB, RAL, and EVG.
2. DTG selects primarily for signature mutations at four positions G118R, Q148HRK, N155H, and R263K. The most common accessory mutations include E138K , T97A, and G140AS. Other less common DRMs include H51Y, T66I, E92Q, and S147G.
3. Fewer data are available for CAB. It selects primarily for 3 of the DTG signature mutations - Q148R, N155H, and R263K. In contrast to DTG, Q148R and N155H are the most common DRMs with R263K occurring less commonly.
4. RAL and EVG have overlapping resistance profiles although RAL uniquely selects for mutations at position 143 while EVG is particularly likely to select for mutations at positions 66, 92, and 147.
5. In the 2-3 case reports of VF with emergent resistance in patients receiving BIC, G118R and R263K have been reported.
6. There have also been 14 studies in which HIV-1 was cultured in the presence of increasing concentrations of one or more INSTI. The DRMs that were selected in these experiments overlap to a large extent with those occurring in patients.

DTG-Associated Signature Mutations



Tao K. Treatment Emergent Dolutegravir Resistance Mutations in Individuals Naïve to HIV-1 Integrase Inhibitors: A Rapid Scoping Review. Viruses 2023

1. This slide shows a much more detailed picture of the patterns of DRMs selected by DTG.
2. It is from a recent review in which we identified 99 previously INSTI-naïve individuals from 37 publications published through August 2023 with VF on a DTG-containing regimen who developed a major nonpolymorphic DRM.
3. Polymorphic and accessory DRMs were identified only when they occurred in an isolate that also contained a major nonpolymorphic DRM.
4. DTG-selected INSTI-associated DRMs clustered into four largely non-overlapping mutational pathways characterized by amino acid mutations at four signature positions: (1) R263K; (2) G118R; (3) N155H; and (4) Q148H/R/K.
5. In fact, 82 (82.8%) of 99 virus sequences contained just one of the signature DRMs. While only 8 virus sequences contained more than one signature DRM.
6. G118R and R263K were significantly negatively correlated with each other and with Q148 mutations and N155H.

In vitro Susceptibility (Phenotypic) Data

Detailed Integrase Phenotype Query

https://hivdb.stanford.edu/cgi-bin/Phenotypes.cgi?Gene=IN

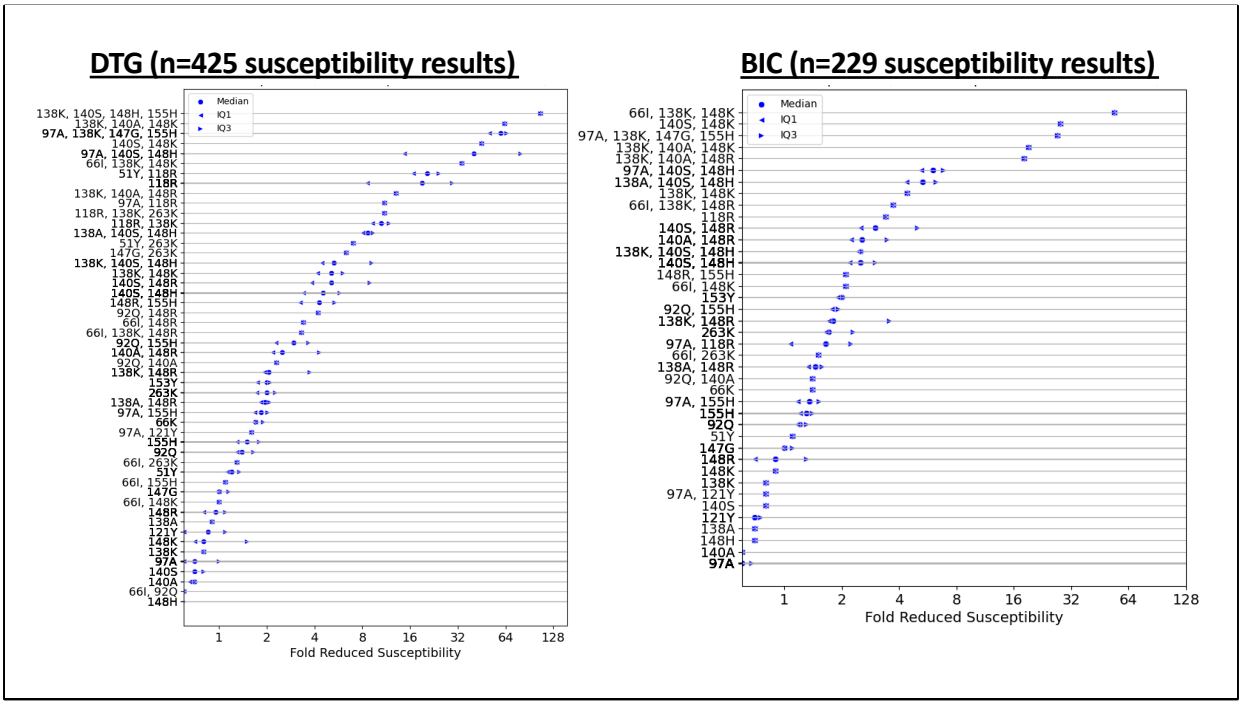
Genotype-Phenotype

Drug	# Phenotypes (PhenoSense / Total)
RAL	1058 / 1658
EVG	1001 / 1549
DTG	415 / 967
BIC	229 / 559
CAB	17 / 427

Page 1 from Isolate 1 to Isolate 5 from Total 5 Isolates

Author (yr)	Type	Isolate	INIMajorDRMs	INIMinorDRMs	Other	Method	Drug	Fold
Tsiang (2016)	Clinical	PT26:G140A_Q148R*	G140A, Q148R			PhenoSense	DTG	2.2
		PT42:L74LM_G140A_Q148R*	G140A, Q148R		L74LM	PhenoSense	DTG	8.8
Andreatta (2018)	Lab	E138K_G140A_Q148R	E138K, G140A, Q148R			PhenoSense	DTG	13
		G140A_Q148R	G140A, Q148R			PhenoSense	DTG	2.8
Eshleman (2022)	Clinical	HPTN083_D4_W37*	G140A, Q148R			PhenoSense	DTG	2.1

1. This figure shows the form for looking up INSTI phenotypic susceptibility data.
2. Two mutations are selected - G140A and Q148R. DTG and the PhenoSense assay are also selected.
3. The figure below shows hos the results are presented with the mutations divided into the categories - Major, Minor, or Other.
4. The fold reduction in susceptibility is shown at the far right.
5. The highest fold reduction of 13 and 8 occur when additional mutations are present - E138K and L74M respectively.
6. Note the asterisk after the the isolate in the first two rows and in the fifth row. This indicates that the complete sequence was not available and so that additional mutations not reported by the author was not reported.
7. Laboratory isolates are site-directed mutants so the mutation list is considered to be complete.
8. The figure on the right shows the total number of susceptibility results in the database for each of the INSTIs according to the type of assay used.
9. We often confine ourselves to the PhenoSense assay because it is highly reproducible and present in the largest numbers in the database.
10. We made an exception for CAB because most the susceptibility data was obtained using assays other than PhenoSense.



1. This slide summarizes the raw in vitro susceptibility data available for DTG and BIC.
2. For each pattern, circles indicate the median value and the left and right triangles indicate the IQR -- when there are 3 or more isolates with the same DRM pattern.
3. The x-axis shows the fold reduction in susceptibility on a log 2 scale.
4. Viruses that have mixtures at one-third or more of their positions were excluded.
5. In addition, not every DRM was used to create a pattern, so there could be some variability as a result of accessory DRM that were not included.
6. For the same DRM pattern, the fold reduction in BIC susceptibility is usually but now always slightly lower for BIC than DTG.
7. For G118R alone, the 7 DTG isolates displayed a 19-fold reduction in susceptibility while the single BIC isolate demonstrated a 3.3-fold reduction
8. For R263K alone, the 10 DTG isolates displayed a 1.7-fold reduction in susceptibility, while for the three BIC isolates, the median fold reduction was 2.0 fold.
9. For G140S/Q148H without other major mutations the median fold reduction in susceptibility for DTG in 24 isolates was 4.6-fold while for BIC in 17 isolates it was 2.6-fold.
10. According to one modeling study report, BIC forms more contacts HIV-1 integrase

than any other INSTI. In that study, the dissociation half life from wildtype IN-DNA complexes was 163 hours for BIC, 96 hours for DTG, 10 hours for RAL, and 3 hours for EVG.

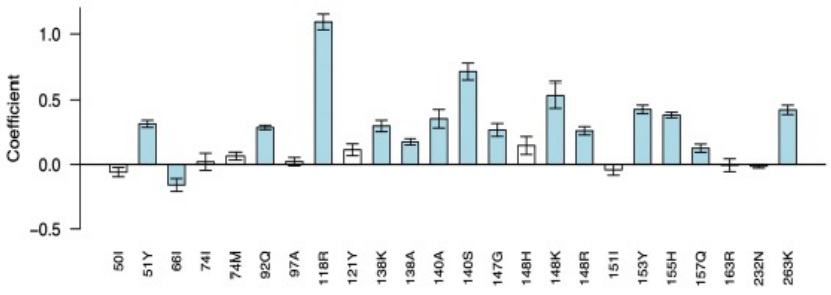
DTG Susceptibility By Signature DRM and Number of Additional DRMs

Signature DRM	# Additional DRMs	# Results	Median Fold Reduced Susceptibility	IQR	Range
G118R	0	2	18.8	14 –23	9.6 – 28
	1	7	22	11 – 29	7.2 – 30
	≥2	5	16	13 – 22	8.0 – 52
R263K	0	7	2.0	1.8 – 2.2	1.5 – 3.3
	1	5	2.1	1.7 – 4.2	1.3 – 7.0
	≥2	1	6.3	6.3	6.3
N155H	0	8	1.4	1.2 – 1.6	1.1 – 2.1
	1	14	1.7	1.5 – 2.0	1.1 – 3.5
	≥2	8	3.1	1.9 – 24	1.5 – 68
Q148H/R/K	0	11	0.8	0.7 – 1.1	0.4 – 1.6
	1	44	3.4	1.9 – 5.5	0.5 – 17
	≥2	27	8.8	3.5 – 15	0.6 – 186

Tao K. Treatment Emergent Dolutegravir Resistance Mutations in Individuals Naïve to HIV-1 Integrase Inhibitors: A Rapid Scoping Review. Viruses 2023

1. This slide simplifies the DTG susceptibilities shown in the previous slide.
2. R263K alone conferred a median 2.0-fold reduction in DTG susceptibility. With ≥1 additional DRM, it conferred a median 3.2-fold reduction in susceptibility. The highest level of reduced susceptibility of an isolate with R263K was 6.3-fold
3. G118R alone conferred a median 18.8-fold reduction in DTG susceptibility). With ≥1 additional DRM, it conferred a median 19.0-fold reduction in susceptibility.
4. N155H alone conferred a median 1.4-fold reduction in DTG susceptibility. With ≥1 additional DRM, it conferred a median 2.0-fold reduction in susceptibility. One isolate with 3 additional non-signature mutations had 68-fold reduced susceptibility but this was uncommon
5. Q148H/R/K alone conferred a median 0.8-fold reduction in DTG susceptibility. With ≥1 additional DRM, they conferred a median 4.1-fold reduction in susceptibility. Several isolates with 148 mutations in combination with mutations at positions 140 and/or 138 and/or additional accessory mutations had high levels of reduced DTG susceptibility.

Effect of DTG-Associated DRMs by Linear Regression

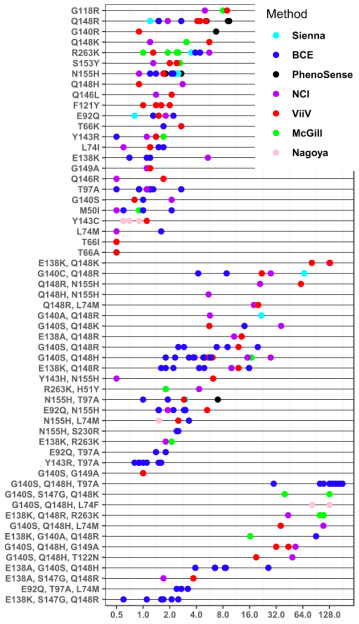


- 26 mutations occurred ≥5 times in the dataset (269 test results).
- Regression coefficients of 14 mutations were associated with ≥1.5-fold reduced susceptibility.
- Including 8 additional DRMs: H51Y, E92Q, E138A/K, G140A/S, S147G, and S153Y.

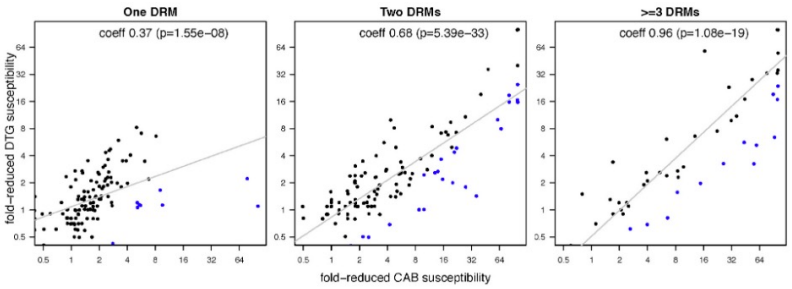
Tao K. Treatment Emergent Dolutegravir Resistance Mutations in Individuals Naïve to HIV-1 Integrase Inhibitors: A Rapid Scoping Review. Viruses 2023

1. Another approach to determining how DRMs influence drug susceptibility, is to create a regression model in which each mutation is an explanatory variable and the fold reduction in susceptibility is the outcome variable..
2. The slide shows which DRMs are predicted to have the greatest effect on DTG susceptibility.
3. It includes only those 26 DRMs that occurred at least 5 times in our dataset.
4. G118R had the greatest effect. Even though G140S has no effect on its own, it usually occurs in combination with Q148 mutations which explains why it has the second greatest effect.
5. Besides the 4 signature mutations, 8 additional DRMs were significantly associated with reduced DTG susceptibility.
6. We haven't performed the same analysis for BIC or CAB because much fewer susceptibility data are available for these two INSTIs.

CAB Susceptibility



Correlation with DTG

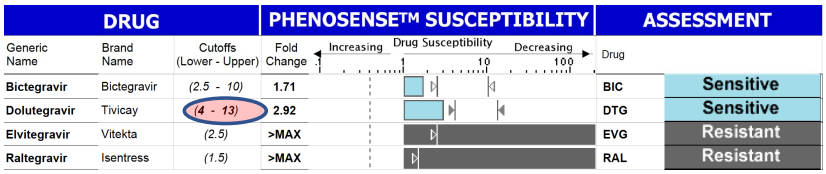


Rhee SY. Genotypic correlates of resistance to the HIV-1 INSTI cabotegravir. Antivir Res 2022

1. The figure on the left summarizes the publicly available phenotypic data for CAB. Only those patterns for which at least 2 results are available are shown.
2. The single mutations with the greatest effects on susceptibility were G118R, Q148R and K, R263K, and N155H. There are conflicting data between the two results on G140R which has been reported in one patient.
3. Reduced susceptibility is unsurprisingly much higher for those viruses containing 2 or more DRMs.
4. The three figures on the right indicate that for similar patterns, the fold resistance for CAB correlated strongly with DTG - especially for viruses containing 2 or ≥3 DRMs with the slope of the lines indicating higher levels of resistance to CAB than DTG for viruses with the same DRMs.

Genotypic and phenotypic predictors of virological response to salvage therapy with DTG-containing regimens (VIKING Trials)

- In the open-label VIKING 3 trial 183 INSTI-experienced participants received DTG 50 mg BID.
- VL <50 at week 24:
  - 79% (100/126) of those without Q148HRK
  - 58% (21/36) with Q148HRK + 1 accessory DRM
  - 24% (5/21) with Q148 + 2 DRMs had a VL<50
- For every 2-fold increase in DTG FC, the odds of achieving VL <50 decreased by 63%.



Castagna A. Dolutegravir in ART-Experienced Patients With RAL- and/or EVG-Resistant HIV-1: 24-Week Results of the Phase III VIKING-3 Study. JID 2014

1. The VIKING trials were the only clinical trials in which patients with baseline INSTI mutations received a second-generation INSTI.
2. The largest of these was the single-arm open-label VIKING-3 trial in which patients with VF and INSTI resistance following treatment with a first-generation INSTI were treated with an optimized regimen containing DTG 50 mg BID
3. The risk of VF was increased in patients containing a Q148 DRM in combination with 1 or 2 additional accessory DRMs. N155H and Y143 DRMs did not increase the risk of VF. There were no patients with baseline R263K or G118R mutations.
4. For every 2-fold increase in DTG FC, the odds of achieving VL <50 decreased by 63%
5. Based on an analysis of data from this trial, Monogram BioSciences established a lower clinical cutoff threshold of 4-fold and an upper clinical cutoff threshold of 13-fold for DTG.
6. The lower clinical cut-off is the fold reduction in susceptibility at which DTG is predicted to be less active than it would be compared to its activity against a wildtype isolate.
7. The upper clinical cut-off is the fold reduction in susceptibility at which DTG is predicted to have little or no impact on suppressing HIV-1 virus load.

8. Pharmacokinetic data were used to extrapolate these thresholds to BIC: 2.5-fold for the lower clinical cutoff and 10-fold for the upper clinical cut-off.

Risk of Emergent DTG Resistance in 6 Clinical Scenarios

Median Prevalence of the Proportions of Clinical Trial Participants Experiencing VF, Undergoing Genotypic Resistance Testing (GRT), and Developing INSTI DRMs in 6 Clinical Scenarios

Clinical Scenario	ART History	Viral Load Prior to DTG	DTG-Containing ART	# Clinical Trials	Median (IQR) # Pts	Median (IQR) % with VF	Median (IQR) % with GRT	Median (IQR) % with INSTI-DRMs
1	Naïve	Viremic	DTG + 2 NRTIs	16	279 (106-410)	4.4 (2.8-6.1)	2.7 (1.0-5.0)	0 (0-0)
2	Naïve	Viremic	DTG + 3TC	4	126 (96-570)	9.4 (3.6-14.3)	1.5 (1.2-2.9)	0 (0-0.6)
3	Experienced	Viremic	DTG + 2 NRTIs	6	217 (183-323)	12.7 (5.3-18.2)	6.6 (3.3-17.4)	1.5 (0.5-3.6)
4	Experienced	Suppressed	DTG + 2 NRTIs	3	275 (205-397)	2.4 (0-5.0)	0 (0-1.5)	0 (0-0)
5	Experienced	Suppressed	DTG + 2nd ARV	10	131 (81-277)	1.7 (0.4-3.0)	1.1 (0-2.3)	0 (0-0)
6	Experienced	Suppressed	DTG monotherapy	4	73 (40-93)	7.8 (1.6-9.8)	7.3 (1.6-8.8)	3.4 (0.7-5.9)

Chu C. Prevalence of Emergent DTG Resistance Mutations in PLWH: A Rapid Scoping Review. Viruses 2024

1. Although there are few data of cases in which 2nd-generation INSTIs have been used for treated patients with INSTI DRMs, there are extensive data demonstrating the efficacy of DTG-containing regimens for treating INSTI-naïve patients.
2. This table shows the prevalence of emergent DRMs in 43 clinical trials encompassing 6 clinical scenarios based on whether patients were ART-naïve or experienced, had active virus replications versus virus suppression and based on the drugs used in combination with DTG.
3. Among several thousand previously ART-naïve patients receiving either DTG + 2 NRTIs or DTG plus 3TC, there was only one case of emergent resistance among the subset of 140 patients with VF undergoing GRT -- clinical scenarios 1 and 2.
4. Among approximately 1000 patients with previous VF on a first-line NNRTI-containing regimen, the overall prevalence of VF with emergent resistance was 1.5% -- clinical scenario 3. Among the subset of 113 patients who experienced VF and had samples undergoing GRT, 20.4% were found to have INSTI DRMs.
5. Among patients with VS, INSTI DRMs occurred only in those receiving DTG monotherapy -- scenario 6. INSTI DRMs did not emerge in the 13 clinical trials of virologically suppressed patients receiving a DTG 2- or 3-drug regimen -- clinical scenarios 5 and 6.

INSTI Notes and Handout

The table lists the most common clinically significant INSTI-resistance mutations. Mutations in bold red are associated with the highest levels of reduced susceptibility or virological response to the indicated INSTI. Mutations in bold reduce INSTI susceptibility or virological response. Mutations in plain text contribute to reduced suceptibility in combination with other INSTI-resistance mutations.

- M50I
- H51Y
- T66A/I/K
- L74M/I/F
- E92Q/G/V
- Q95K
- T97A
- G118R
- F121Y
- E138K/A/T
- G140S/A/C/R
- Y143C/R/H/K/S/G/A
- P145S
- Q146P
- S147G
- Q148H/K/R/N
- G149A
- V151I/L/A
- S153Y/F/A
- N155H/S/T/D
- E157Q
- G163R/K
- S230R
- D232N
- R263K
- Non-Integrase Mutations

M50I

M50I is a highly polymorphic mutation, which has a prevalence of 3% to 34% in INSTI-naïve persons depending on subtype. It has been selected in vitro by DTG and BIC in combination with R263K (1,2). It may contribute to reduced DTG susceptibility in combination with R263K in one study (3).

H51Y

H51Y is an uncommon nonpolymorphic accessory mutation. It is selected in vitro by EVG (4,5,6), DTG (1,7,8,9), CAB (9) and in vivo by RAL (10), EVG (11), and DTG (12). Alone, it reduces EVG susceptibility by 2-3-fold (4,6,13,14,15) but alone does not appear to reduce susceptibility to any of the other INSTIs (6,13,14,15).

T66A/I/K

T66A/I/K are nonpolymorphic mutations primarily selected in patients receiving EVG and RAL (10,11,16,17,18,19). T66A/I reduce EVG susceptibility 5-10-fold but have minimal effect on other INSTIs (4,6,20,21,22). T66K reduces EVG susceptibility ~40-fold, RAL susceptibility ~10-fold, and CAB and DTG susceptibility by 2-3-fold (6,20,22).

L74M/I/F

L74M is a common polymorphic INSTI-resistance mutation. It has a prevalence between 1% and 5% among INSTI-naive persons depending on subtype. It appears to be selected by each of the INSTIs (23). Alone it does not reduce INSTI susceptibility. However, in combination with other INSTI-resistance mutations, it significantly reduces susceptibility to each of the INSTIs (2,24,25,26).

L74I is a highly polymorphic mutation with a prevalence of 3% to 30% depending on subtype. It is the consensus amino acid in subtype A viruses belonging to the A6 clade. In contrast to L74M, L74I is not more common in persons receiving INSTIs compared with in INSTI-naïve persons (23) nor has it been shown to reduce susceptibility to any of the INSTIs either alone or in combination with other mutations (26,27).

https://hivdb.stanford.edu/dr-summary/resistance-notes/INSTI/

Major Integrase Inhibitor (INSTI) Resistance Mutations

	66	92	118	138	140	143	148	155	263
Cons	T	E	G	E	G	Y	Q	N	R
BIC	K	Q	**R**	KAT	SAC		**HRK**	H	**K**
CAB	K	Q	**R**	KAT	SAC**R**		**HRK**	**H**	**K**
DTG	K	Q	R	KAT	SAC		**HRK**	H	**K**
EVG	**AIK**	**Q**	**R**	**KAT**	**SAC**		**HRK**	**H**	**K**
RAL	AI**K**	**Q**	**R**	**KAT**	**SAC**	**RCH**	**HRK**	**H**	K

Bold underline: High-level reduced susceptibility or virological response. **Bold**: Low-level reduced susceptibility or reduced suceptibility or virological response. Plain text: Rreduced susceptibility in combination with other INSTI-resistance mutations.

Abbreviations: Bictegravir (BIC), dolutegravir (DTG), cabotegravir (CAB), elvitegravir (EVG), raltegravir (RAL).

Additional mutations: T97A is a polymorphic mutation (1%-4%) in INSTI-naive patients. In combination with Q148 + G140/E138 DRMs, it causes high-level BIC/DTG resistance. H51Y, F121Y, S147G, S153YF, and S230R are additional nonpolymorphic INSTI DRMs. E92GV, Y143HKSGA, P145S, Q146LP, Q148N, G149A, V151AL, and N155ST are rare nonpolymorphic IN mutations that reduce RAL and/or EVG susceptibility. L74M, V151I, E157Q, G163KR, and D232N are common polymorphic accessory DRMs. Mutations outside of IN in the polypurine tract have also rarely been reported to reduce INSTI susceptibility.

https://cms.hivdb.org/prod/downloads/resistance-mutation-handout/resistance-mutation-handout.pdf

1. The data that I reviewed in this presentation are summarized to a large extent in the Notes section of the HIV GRT interpretation program and in a very brief format in a PDF handout.
2. No major changes were made to the Notes and PDF handout since October 2022.

Individual DRM Scores

Rule	BIC	CAB	DTG	EVG	RAL
G118R	30	60	50	60	60
R263K	30	30	30	30	25
Q148K	30	50	30	60	60
Q148R	25	40	25	60	60
Q148H	25	30	25	60	60
S230R	10	20	20	20	20
S153Y	15	25	15	25	10
S153F	15	25	15	25	10
V151L	15	15	15	60	30
F121C	15	60	15	60	60
T66K	15	20	15	60	60
N155H	10	25	10	60	60
S147G	10	10	10	60	10
G140S	10	10	10	30	30
G140R	10	60	10	30	30
G140C	10	10	10	30	30
G140A	10	10	10	30	30
E138T	10	10	10	15	15
E138K	10	10	10	15	15
E138A	10	10	10	15	15
F121Y	10	15	10	60	60
E92Q	10	15	10	60	30
H51Y	10	15	10	15	15

Rule	BIC	CAB	DTG	EVG	RAL
Y143S	5	10	5	10	60
Y143R	5	10	5	10	60
Y143K	5	10	5	10	60
Y143H	5	10	5	10	60
Y143G	5	10	5	10	60
Y143C	5	10	5	10	60
Y143A	5	10	5	10	60
T66I	5	10	5	60	15
D232N	0	0	0	10	10
G163R	0	0	0	15	15
G163K	0	0	0	15	15
E157Q	0	0	0	10	10
V151A	0	0	0	30	15
P145S	0	0	0	60	0
T97A	0	0	0	10	10
Q95K	0	0	0	10	10
T66A	0	0	0	60	15
N155T	0	15	0	30	30
N155S	0	15	0	30	30
Q148N	0	15	0	15	15
Q146P	0	30	0	60	0
E92V	0	10	0	60	30
E92G	0	10	0	30	15

Combination DRM Scores

Combination Rule	BIC	CAB	DTG	EVG	RAL
G118R + E138AKT	10	10	10	10	10
E138AKT + G140ACS	10	15	10	15	15
E138AKT + Q148HKR	10	20	10	0	0
G140ACS + Q148HKR	10	20	10	0	0
G140ACS + Q148HKR + G149A	10	10	10	10	10
Y143ACGHRS + G163R	5	5	5	5	0
Y143ACGHRS + S230R	5	5	5	5	0
S147G + Q148HKR	15	20	15	0	0
S147G + N155H	10	25	10	10	0
Q148HKR + N155H	20	20	20	0	0
Q148HKR + G163KR	5	20	5	0	0
N155H + R263K	20	20	20	0	0
E157Q + R263K	10	10	10	0	0
H51Y + R263K	10	10	10	15	0
L74FIM + G118R	10	10	10	10	10
L74FIM + Y143ACGHRS	5	10	5	5	0
L74FIM + Q148HKR	15	15	15	15	15
E92Q + N155H	10	20	10	10	10
T97A + G118R	10	10	10	10	10
T97A + Q148HKR	15	20	15	0	0
T97A + Y143ACGHRS	0	5	0	5	0

https://hivdb.stanford.edu/dr-summary/mut-scores/INSTI/

1. The HIVDB website also contains a list of all scores, which were last updated March 2024
2. There are individual mutation penalty scores for nearly all DRMs and several penalties that go into effect only when certain DRM combinations are present.
3. The total mutation penalty score for a drug is based on adding all of the individual and combination penalty scores.

INSTI Comments

Condition	Comment/ Mutation Type	Comment
74M	Accessory	L74M is a common polymorphic INSTI-resistance mutation. It has a prevalence between 1% and 5% among INSTI-naive persons depending on subtype. It appears to be selected by each of the INSTIs. Alone it does not reduce INSTI susceptibility. However, in combination with other INSTI-resistance mutations, it contributes reduced susceptibility to each of the INSTIs.
97A	Accessory	T97A is a polymorphic INSTI-selected mutation that, depending on subtype, occurs in 1% to 5% of viruses from untreated persons. Alone, it has minimal effects on INSTI susceptibility but in combination with other major resistance mutations, it synergistically reduces susceptibility to each of the INSTIs.
118R	Major	G118R is a nonpolymorphic mutation reported in a significant proportion of persons with VF and emergent HIVDR in persons receiving a DTG-containing regimen. It has occasionally been reported in persons receiving other INSTIs. It is associated with 5-10-fold reduced susceptibility to RAL, EVG, DTG and CAB, and 2-3 fold reduced susceptibility to BIC.
148HKR	Major	Q148H/K/R are nonpolymorphic mutations reported in persons receiving RAL, EVG, CAB, and DTG. They nearly always occur in combination with G140A/S or E138K. In this setting they are associated with near complete resistance to RAL and EVG, high-levels of reduction in CAB susceptibility, and low-to-intermediate reductions in DTG and BIC susceptibility.
155H	Major	N155H is a common nonpolymorphic INSTI-resistance mutations. It has been reported in a high proportion of persons developing VF and HIVDR while receiving RAL, EVG, DTG, and CAB. Alone, it reduces RAL and EVG susceptibility about 10 and 30-fold, respectively. It has minimal effect on susceptibility to DTG, BIC, and CAB.
263K	Major	R263K is a nonpolymorphic mutation selected in vitro by EVG, DTG, BIC, and CAB. It occurs in a high proportion of persons who develop VF and emergent HIVDR while receiving DTG. Alone, it reduces DTG, BIC, and CAB susceptibility about 2-fold.
138KAT	Major	E138K/A/T are common nonpolymorphic accessory resistance mutations selected in patients receiving RAL, EVG, CAB, and DTG. Alone they do not reduce INSTI susceptibility. However, they contribute to reduced susceptibility in combination with other mutations particularly those at position 148.
140R	Major	G140R is a nonpolymorphic mutation reported in n macaques receiving CAB pre-exposure prophylaxis and in a person receiving simplification therapy with RPV/CAB. It can reduce CAB susceptibility up to 7-fold.
140SAC	Major	G140S/A/C are non-polymorphic mutations that usually occur with Q148 mutations. Alone, they have minimal effects on INSTI susceptibility. However, in combination with Q148 mutations they are associated with high-level resistance to RAL and EVG and intermediate reductions in DTG and BIC susceptibility.

https://hivdb.stanford.edu/dr-summary/comments/INSTI/

1. All DRMs that receive a mutation penalty score and some that don't are accompanied by a comment.
2. The complete list of comments for each drug class can be viewed on the website
3. The comments have last been updated March 2024

Pre-Computed Scores for All DRM Patterns

Pattern	# Sequences	BIC	CAB	DTG	EVG	RAL
L74I	2948	0	0	0	0	0
E157Q	909	0	0	0	10	10
T97A	512	0	0	0	10	10
L74M	465	0	0	0	0	0
G140S + Q148H	324	45	60	45	90	90
N155H	302	10	25	10	60	60
D232N	202	0	0	0	10	10
G163R	161	0	0	0	15	15
L74I + T97A	74	0	0	0	10	10
E138K	73	10	10	10	15	15
R263K	71	30	30	30	30	25
L74I + E157Q	69	0	0	0	10	10
E92Q	68	10	15	10	60	30
N155H + D232N	67	10	25	10	70	70
G163K	64	0	0	0	15	15
L74M + T97A	62	0	0	0	10	10
Q148R	52	25	40	25	60	60
Q95K	51	0	0	0	10	10
N155H + G163R	50	10	25	10	75	75
E92Q + N155H	49	30	60	30	130	100

https://hivdb.stanford.edu/dr-summary/pattern-scores/INSTI/

1. There is also a table that lists precomputed scores for all combinations of DRMs present in the database.
2. The table can be sorted by the # sequences so that the most common DRM patterns are shown at the top or by those DRMs associated with the highest scores for an INSTI.
3. It is very useful for us to check this table to make sure that updates to the mutation penalty scores lead to the results intended for actual virus isolates

Mutations Associated with Reduced Susceptibility to INSTIs

For questions and suggestions:
hivdbteam@lists.Stanford.edu

1. Thank you for your attention.
2. If you have any questions or suggestions don't hesitate to email us.