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Prevalence of Integrase HIV-1 Drug Resistance Mutations in the United States: 2019-2024

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Key Takeaways

- **Among HIV-1 samples tested for genotypic resistance, the prevalence of reduced susceptibility to the integrase inhibitor class was low and stable between 2019 and 2024**
- **Individual major integrase inhibitor resistance mutations were present in low frequencies throughout the study period**

Introduction

- The integrase strand transfer inhibitor (INSTI) antiretroviral (ARV) class, specifically second-generation INSTIs (dolutegravir, bictegravir, and cabotegravir), has been increasingly used in HIV-1 treatment due to high levels of effectiveness and tolerability, improved adherence, and high barriers to resistance[1-3]
- At the population level, ARV use patterns can impact prevalence of HIV-1 drug resistance[3,4]
- This analysis used data from a large, representative, commercial testing database to assess changes in INSTI resistance mutation frequencies and class-level susceptibility with expanding use in the United States from 2019-2024
- A previous analysis using the same data source to evaluate trends in INSTI prevalence for the period of 2012-2018 found that resistance to the INSTI class declined after 2013, and remained relatively low and stable (14%-17%) among samples with resistance detected from 2014-2018[5]

Methods

Sample Collection

- HIV-1 samples were collected from adults aged ≥18 years in the United States or US territories between January 1, 2019, and December 31, 2024, as part of routine clinical care
- For individuals with multiple samples, a maximum of 1 sample per calendar year (the most recent sample) was included in the analysis

Resistance Testing

- Samples were collected and then de-identified and tested for HIV-1 RNA using Monogram Bioscience's GenoSure PRIme® assay
  - GenoSure PRIme tests for genotypic resistance to 4 classes of HIV-1 drugs: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and INSTIs[6]
- Basic demographic information was reported with each sample: participant age, gender, and region of collection site
  - No other demographic or clinical information were linked to the samples
  - INSTI class resistance was defined as reduced susceptibility to at least one ARV in the class
  - Reduced susceptibility was predicted by Monogram's proprietary HIV-1 genotypic algorithm, which is based on >100,000 matched HIV genotype-phenotype results

Data Analysis

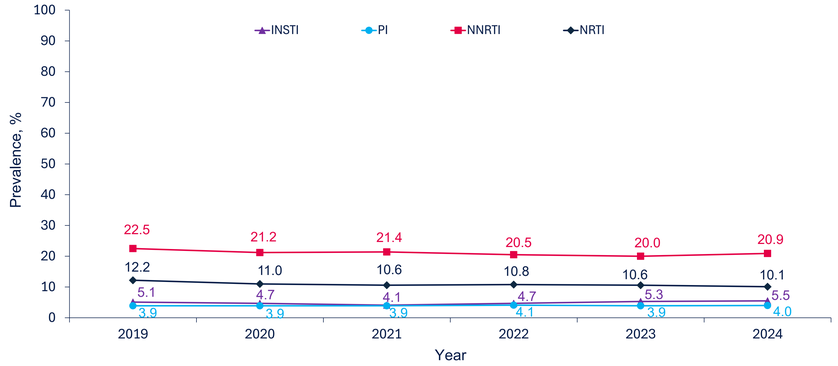
- Results were assessed using descriptive statistics and 2 denominators for proportions:
  - All submitted samples
  - Samples demonstrating genotypic resistance to at least 1 ARV in 1 ARV class; to minimize bias introduced by changes to resistance testing behaviors and sample submission over time
- Individual drug resistance mutations were identified and classified as major or minor based on impact to drug susceptibility[7,8]

Results

ARV Class Resistance Prevalence

- 104,074 samples were evaluated
- INSTI resistance ranged between 4.1% to 5.5% of all tested samples across years (Figure 1)

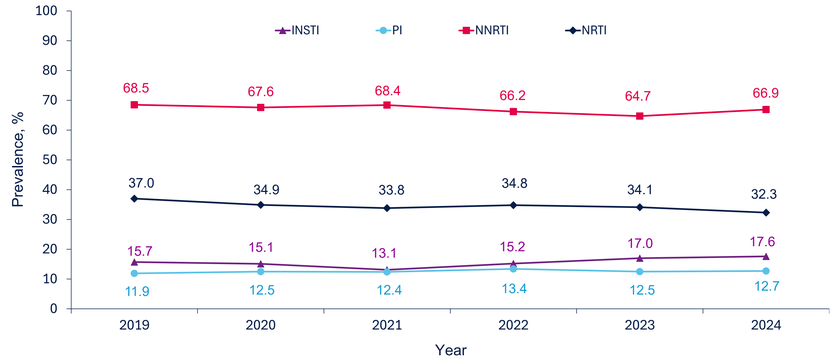
Figure 1. Prevalence of ARV Class Resistance Among All Eligible Samples Submitted for Testing[a]



[a]Class resistance is defined as reduced susceptibility detected by GenoSure Prime assay to at least one drug within the specified ARV class. Samples were classified as sensitive or resistant to individual drugs based on a proprietary Monogram resistance algorithm that is based on a database of more than 100,000 matched genotype-phenotype results.

- Among 32,761 (31.5%) of samples with any resistance, 15.6% (n=5099) demonstrated reduced susceptibility to ≥1 INSTI (range:13.1%-17.6% across years; Figure 2)

Figure 2. Prevalence of ARV Class Resistance Among Eligible Samples With Resistance Detected to at Least 1 ARV, 2019-2024[a]



[a]Class resistance is defined as reduced susceptibility detected by GenoSure PRIme assay to at least one drug within the specific ARV class. Samples were classified as sensitive or resistant to individual drugs based on a proprietary resistance algorithm that is based on a database of more than 100,000 matched genotype-phenotype results.

- The prevalence of INSTI resistance varied across demographic groups (Table 1)
  - Prevalence increased proportionately with age and was highest in the Northeast United States and US territories

Table 1. Frequency and Proportion of Samples With INSTI Resistance Within Each Demographic Category, 2019-2024

Category	Samples with INSTI resistance, n (%)
Age group, years	
18-25	372 (3)
26-35	1295 (3)
36-45	1177 (5)
45-55	1133 (6)
56-65	860 (7)
>65	235 (7)
Gender	
Female	1309 (6)
Male	3752 (5)
Unknown	38 (5)
Region[a]	
Midwest	379 (5)
Northeast	1346 (6)
South	2712 (5)
West	653 (4)
Other	9 (8)

[a]Midwest: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, South Dakota, Wisconsin; Northeast: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont; South: Alabama, Arkansas, Delaware, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, Washington, DC, West Virginia; West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming; Other: Puerto Rico, Virgin Islands, unknown.

Major Mutation Frequency in the Integrase Gene

- Prevalence estimates for individual major mutations impacting susceptibility to drugs within the INSTI class were very low across all years (Table 2)
- Most mutations were stable, with small declines in N155H (2019-2024: 0.82%-0.6%) and some variants impacting first-generation INSTIs (raltegravir, elvitegravir; E92Q [1.04%-0.37%], T66I [0.14%-0.06%], Y143R [0.14%-0.05%])
  - R263K showed increasing frequency (0.42%-1.7%) but remained uncommon

Table 2. Major Mutation Frequency in the Integrase Gene Associated With Resistance to Integrase Inhibitors, 2019-2024

INSTI mutations n (%)	2019 samples N=20,869	2020 samples N=16,425	2021 samples N=17,732	2022 samples N=16,459	2023 samples N=15,676	2024 samples N=16,913
T66I[a]	29 (0.14)	30 (0.18)	20 (0.11)	16 (0.1)	16 (0.1)	10 (0.06)
T66A[a]	18 (0.09)	13 (0.08)	13 (0.07)	12 (0.07)	11 (0.07)	6 (0.04)
T66K[a]	0 (0)	2 (0.01)	1 (0.1)	1 (0.01)	1 (0.01)	1 (0.01)
E92Q[a]	216 (1.04)	104 (0.63)	84 (0.47)	48 (0.29)	67 (0.43)	62 (0.37)
G118R	6 (0.03)	17 (0.1)	17 (0.1)	16 (0.1)	21 (0.13)	20 (0.12)
G140A[a]	10 (0.05)	11 (0.07)	8 (0.05)	12 (0.07)	14 (0.09)	19 (0.11)
G140C[a]	10 (0.05)	5 (0.03)	6 (0.03)	8 (0.05)	7 (0.04)	13 (0.08)
G140R	0 (0)	1 (0.01)	1 (0.01)	1 (0.01)	0 (0)	0 (0)
G140S[a]	118 (0.57)	93 (0.57)	72 (0.41)	97 (0.59)	89 (0.57)	91 (0.54)
Y143C[a]	12 (0.06)	12 (0.07)	2 (0.01)	12 (0.07)	7 (0.04)	6 (0.04)
Y143H[a]	11 (0.05)	3 (0.02)	3 (0.02)	3 (0.02)	5 (0.03)	5 (0.03)
Y143R[a]	29 (0.14)	18 (0.11)	15 (0.08)	18 (0.11)	8 (0.05)	8 (0.05)
S147G[a]	107 (0.51)	77 (0.47)	70 (0.39)	66 (0.4)	63 (0.4)	78 (0.46)
Q148H	109 (0.52)	88 (0.54)	65 (0.37)	84 (0.51)	76 (0.48)	74 (0.44)
Q148K	6 (0.03)	2 (0.01)	8 (0.05)	6 (0.04)	17 (0.11)	19 (0.11)
Q148R	63 (0.3)	38 (0.23)	39 (0.22)	56 (0.34)	57 (0.36)	65 (0.38)
N155H	172 (0.82)	118 (0.72)	107 (0.6)	111 (0.67)	90 (0.57)	102 (0.6)
R263K	88 (0.42)	72 (0.44)	79 (0.45)	136 (0.83)	202 (1.29)	287 (1.7)

[a]Major mutations associated with reduced susceptibility or virological response to first-generation INSTIs (raltegravir and elvitegravir).

Conclusions

- From 2019-2024, the prevalence of INSTI resistance among samples collected in the United States and US territories was relatively low (4.1%-5.5%) and stable despite increased and widespread use of drugs in the INSTI class within this period
- Prevalence of INSTI resistance among samples with any detected resistance was stable, with similar estimates between 2014-2018 (14%-17%) and 2019-2024 (13%-18%)
- Individual mutations associated with the highest levels of reduced susceptibility or virologic response (major mutations) were infrequent across the analysis period
- The low and stable prevalence estimates for resistance to the INSTI class and individual INSTI drug-resistant mutations were consistent with other analyses of HIV-1 specimens submitted for routine genotypic resistance testing in the United States (2018-2024)[9]
- Observed trends reflect greater use of second-generation INSTIs, which have low failure rates and high barriers to resistance

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