TRENDS AND CHARACTERISTICS OF HIV-1 DRUG RESISTANCE IN THE UNITED STATES (2012-2018)

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Introduction

- The prevalence of transmitted and acquired HIV-1 drug resistance impacts effectiveness of antiretroviral therapy in both treatment-naive and treatment-experienced people living with HIV.[1]
- Given the relatively recent availability of integrase inhibitors (INSTIs) for treatment of HIV, there have been few studies of trends in prevalence of 4-class resistance [INSTIs, protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs)].[2,3]
- This analysis utilized data from a large, representative commercial patient testing database to assess trends in HIV-1 resistance prevalence in the modern treatment era.

Methods

- De-identified HIV-1 samples submitted for routine HIV resistance testing with Monogram Biosciences' GenoSure PRIme® assay were analyzed.
  - GenoSure PRIme tests for genotypic resistance to 4 classes of HIV drugs: NRTIs, NNRTIs, PIs, and INSTIs.
  - GenoSure PRIme is used to assess both transmitted and acquired HIV resistance.
- Samples collected from individuals in the United States or US territories between July 1, 2012 (first availability of test), and June 30, 2018 (database cut-off), were included in the analysis.
- Per individual subject, a single test per year could be reported, allowing for individuals to contribute data from multiple tests between years, but not within the same year.
- To minimize bias by sample submission trends as a result of changes in resistance testing behaviors over time, the analysis was restricted to samples demonstrating substantial genotypic resistance to at least one ARV in any class (PI, NRTI, NNRTI, or INSTI). Substantial decreased susceptibility was predicted by Monogram's proprietary HIV-1 genotypic algorithm, which is based on >100,000 matched HIV-1 genotype-phenotype results.
- Class resistance was defined as reduced susceptibility to at least one drug within the class.

Results

- A total of 84,611 eligible samples were evaluated during the study period.
- Of these, 27,911 (33.0%) demonstrated reduced susceptibility to at least one ARV.
- Between 2012-2018, reduced susceptibility to at least one NNRTI was most common and consistent (~75%) in samples with any resistance. Resistance to NRTIs and PIs steadily declined over the study period; INSTI resistance decreased (2012-2014), and then stabilized (2014-2017) (Figure 1).

Figure 1. Prevalence of class resistance among samples with resistance, 2012-2018

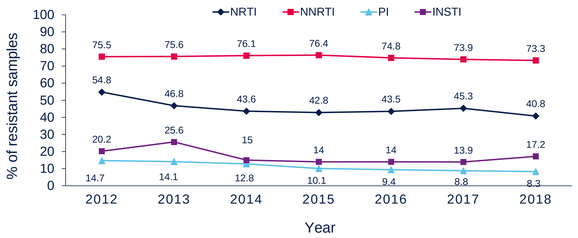


Figure 2. Prevalence of multi-class resistance among samples with resistance, 2012-2018

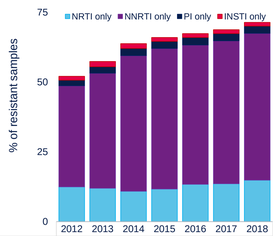
- Resistant samples were increasingly resistant to a single class, with corresponding decreases in 2-, 3-, and 4-class resistance (Figure 2).

Figure 3. 1-, 2-, 3-, and 4-class resistance by demographic characteristics

Other: Puerto Rico, Guam, Virgin Islands, or unknown.

Figure 4. Class-specific resistance among samples with 1-, 2-, 3-, and 4-class resistance

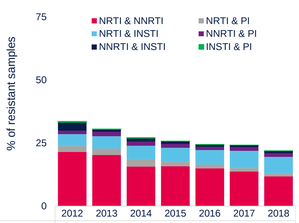
4a. 1-class resistance



	2012	2013	2014	2015	2016	2017	2018
INSTI only	1.4	1.9	1.7	1.4	1.4	1.4	1.3
PI only	2	2.3	2.6	2.5	2.7	2.6	2.6
NNRTI only	36.2	41.2	48.6	50.4	49.9	51.2	52.6
NRTI only	12.5	12	10.9	11.7	13.4	13.6	14.9

% of samples with specific 1-class resistance.

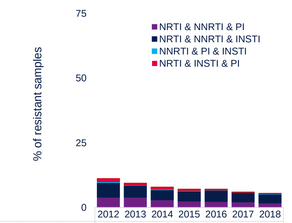
4b. 2-class resistance



	2012	2013	2014	2015	2016	2017	2018
INSTI & PI	0.4	0.2	0.30	0.1	0.1	0.03	0.1
NNRTI & INSTI	3.3	1	1.3	1.1	0.9	0.9	0.9
NNRTI & PI	1.4	1.7	1.7	1.5	1.3	1.4	1.5
NRTI & INSTI	4.7	4.9	5.3	5.6	5.7	6.8	6.7
NRTI & PI	2.3	2.5	2.9	1.7	1.5	1.4	1
NRTI & NNRTI	21.5	20.3	15.7	15.8	15	13.7	11.8

% of samples with specific 2-class resistance.

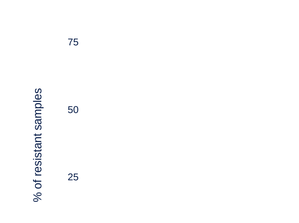
4c. 3-class resistance



	2012	2013	2014	2015	2016	2017	2018
NRTI & INSTI & PI	1.2	0.7	0.8	0.6	0.4	0.2	0.2
NNRTI & PI & INSTI	0.4	0.2	0.3	0.2	0.1	0.1	0.2
NRTI & NNRTI & INSTI	5.7	4.6	3.9	3.9	4.3	3.6	3.4
NRTI & NNRTI & PI	3.9	3.9	2.9	2.4	2.3	2.1	1.7

% of samples with specific 3-class resistance.

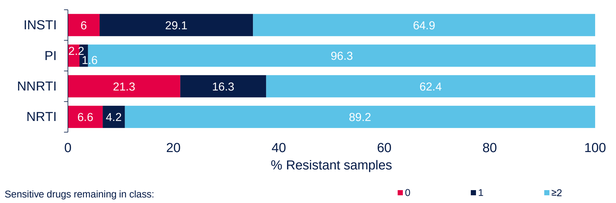
4d. 4-class resistance



	2012	2013	2014	2015	2016	2017	2018
NRTI & NNRTI & PI & INSTI	3.1	2.6	1.6	1.2	1	0.9	1.1

% of samples with 4-class resistance.

Figure 5. Extent of within class resistance among samples resistant to at least 2 ARV drug classes



- Multiclass (≥2 classes) resistance increased with older age. Samples from US territories were more likely to have multiclass resistance compared to samples from US geographic regions (Figure 3).
- Increases in samples with single-class resistance were primarily associated with an increasing proportion of single-class NNRTI resistance (Figure 4).
- Resistance to INSTIs was uncommon and decreasing over time, particularly in combination with resistance to other core agent classes (PIs and NNRTIs).
- Even with documented class resistance, most samples remained susceptible to at least one ARV drug within the resistant class (Figure 5).

Discussion

- The prevalence of 2-, 3-, and 4-class resistance declined from 2012-2018.
- Four-class resistance was rare across the study period.
- Samples with resistance to drugs in a particular class commonly remained susceptible to other drugs in the class, particularly for ARV classes with high potency and high barriers to resistance/low cross-resistance.
- While those with extensive resistance across and within drug classes made up a small proportion of people living with HIV, these individuals are in great need of novel treatment options.
- The large Monogram dataset of real-world test results used is well-suited to provide insights into temporal trends with modern ARVs, including INSTIs.
- In this dataset, we were unable to distinguish between transmitted and acquired resistance mutations. Additionally, prevalence of specific mutations and susceptibility to individual drugs within each class were not analyzed.

Conclusions

- Decreasing prevalence of multiclass ARV resistance was observed in testing data, in addition to declines in NRTI, PI, and INSTI resistance.
- These trends correspond with the availability of newer treatment options with favorable cross-resistance profiles, improved effectiveness, and more convenient formulations leading to better adherence

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References: 1. Poon et al. Transmitted drug resistance in the CFAR network of integrated clinical systems cohort: prevalence and effects on pre-therapy CD4 and viral load. *PLoS One.* 2011;6(6):e21189. **2.** Paquet et al. A decade of HIV-1 drug resistance in the United States: trends and characteristics in a large protease/reverse transcriptase and co-receptor tropism database from 2003 to 2012. *Antivir Ther.* 2014;19(4):435-441. **3.** Mauskopf et al. Systematic literature review of multiclass resistance in heavily treatment experienced persons with HIV. *Open Forum Infect Dis.* 2019;6(suppl 2):S871.