HIV-1 Drug Resistance Trends in the Era of Modern Antiretrovirals: 2018-2024

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Introduction

Transmitted or acquired antiretroviral (ARV) drug resistance limits treatment options for people living with HIV-1 and may reduce the effectiveness of preexposure prophylaxis (PrEP).[1-3] Novel treatment options with enhanced effectiveness and more convenient formulations have become available from 2016 to 2021. In addition, long-acting ARVs (LA-rilpivirine + LA-cabotegravir) and LA-cabotegravir for PrEP are now in routine clinical use. There are few recent studies of the prevalence of drug resistance. This study utilized a large and representative US national reference laboratory database to assess the prevalence of ARV drug resistance for both plasma RNA and proviral DNA testing between 2018 and 2024.

Methods

The study included deidentified sequences from US patients between the ages of 1 and 90 submitted for routine plasma RNA (N>50,000; Sanger sequencing) and proviral DNA (N>25,000; next generation sequencing) clinical testing between January 2018 and May 2024.

The annual prevalences of drug resistance mutations (DRMs) with a Stanford HIV database v9.6 score of ≥30 for nucleoside reverse transcriptase inhibitors (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and integrase strand transfer inhibitors (INSTI) were analyzed.

Resistance trends were evaluated by year, patient age and by US HHS region.

Results

Most specimens tested were from men (RNA: 76.3%; DNA: 78.6%) and the median [IQR] age of patients undergoing DNA testing was higher (RNA: 41 [31 – 53]; DNA: 51 [38 – 59]). Most sequences (RNA: 93.9%; DNA: 95.3%) were classified as HIV-1 subtype B and the most frequent non-B subtypes were AG, C, AE, BF, and BG.

Resistance to any NRTI, NNRTI, PI or INSTI declined significantly (Cochran-Armitage test; p<0.0001) from 2018 to 2024 for both plasma RNA and DNA sequences (**Figure 1**). DRM prevalence was higher for DNA compared to RNA sequences at the clinically reportable minority variant (MV) cutoff of 10%. However, when the MV cutoff was increased to 20% to approximate the sensitivity of Sanger sequencing, the trends were similar (**Figure 1**).

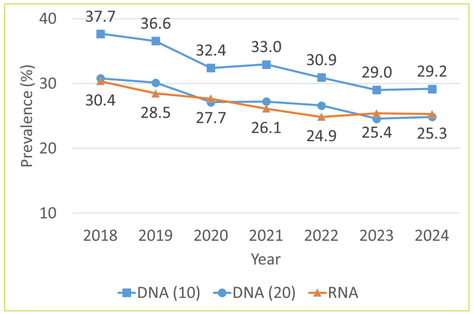


Figure 1. Prevalence of Resistance in HIV-1 Plasma RNA and pvDNA Specmens from 2018 - 2024. NRTI, NNRTI, PI or INSTI DRMs with a Stanford DB score ≥30 were included. DNA (10): DNA DRMs at the clinical MV cutoff of 10%. DNA (20): DNA DRMs at an MV cutoff of 20%; RNA: plasma RNA DRMs detected by Sanger sequencing.

Results (continued)

Dual-class resistance prevalence for the NRTIs combined with either NNRTIs or INSTIs declined for both plasma RNA and proviral DNA sequences from 2018 to 2024 (**Figure 2**). However, dual and triple-class resistance were identified more frequently in older adults (**Figure 3**). PI resistance remained uncommon in RNA specimens with prevalences between 2.5% and 2.9% and declined from 5.3% to 2.1% in DNA specimens (not shown).

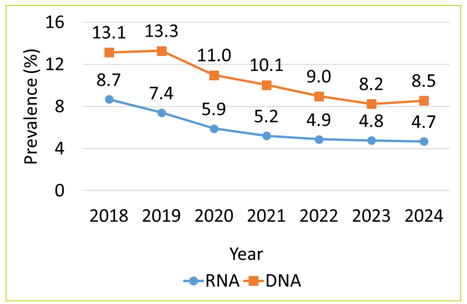


Figure 2. Dual-class resistance for NRTI + NNRTI or NRTI + INSTI for RNA and DNA specimens. DNA DRMs (Stanford HIV DB score ≥30) were analyzed at the 10% clinical MV cutoff.

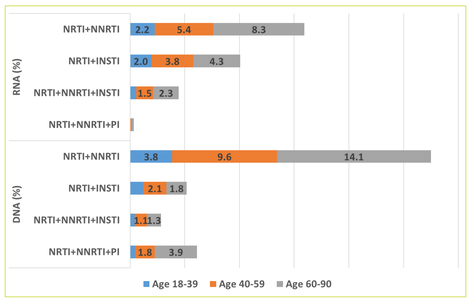


Figure 3. Dual- and triple-class resistance by patient age group for RNA and DNA specimens. DRMs with a Stanford HIV DB score ≥30 were tabulated for each category. A 10% MV cutoff was used for DNA sequences.

Prevalence of DRMs for the newest NNRTI Doravirine and for the NNRTI rilpivirine that is being increasingly used in long-acting formulations, remained low or slightly declined, with respective 2024 prevalences of 2% (RNA) and 2.9% (DNA) and 6.3% (RNA) and 10.1% (DNA) (**Figure 4**).

DRM prevalence for the newest INSTI cabotegravir remained low or slightly declined to 3.8% (RNA) and 2.5% (DNA) in 2024 (**Figure 5**). Although low, prevalence of R263K increased over time in RNA and DNA (**Table 1**).

Results (continued)

Table 1. Prevalence of INSTI Signature DRMs

	INSTI (RNA, %)[a]			INSTI (DNA, %)		
Year	Q148H/K/R	N155H/T	R263K	Q148H/K/R	N155H/T	R263K
2018	2.1	2.2	0.5	0.8	0.6	0.3
2019	1.8	1.6	0.6	0.9	0.9	0.3
2020	1.7	1.7	0.9	0.8	0.9	0.4
2021	1.5	1.2	1.1	0.6	0.8	0.5
2022	1.4	0.9	1.2	0.6	0.8	0.6
2023	1.6	1.1	1.0	0.5	0.6	0.6
2024	1.2	1.0	1.5	0.7	0.8	0.6

[a]Mutations were tabulated for all sequences tested for INSTI resistance.

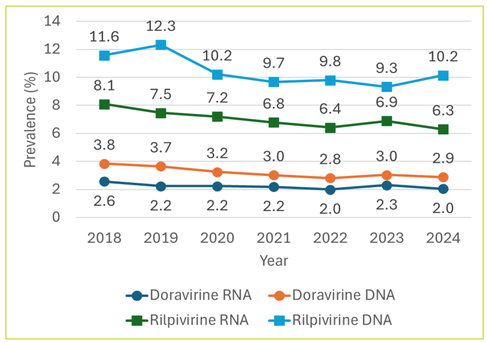


Figure 4. Doravirine and Rilpivirine DRM prevalence in RNA and DNA sequences. Doravirine and rilpivirine DRMs with a Stanford HIV DB score ≥30 were tabulated. A 10% MV cutoff was used for DNA sequences.

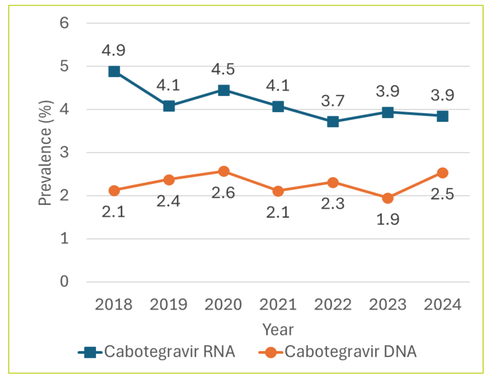


Figure 5. Cabotegravir DRM prevalence in RNA and DNA sequences. Cabotegravir DRMs with a Stanford HIV DB score ≥30 were tabulated. A 10% MV cutoff was used for DNA sequences.

Results (continued)

Prevalence of K65R/N, associated with resistance to NRTIs abacavir and tenofovir, declined to less than 1% in 2024 for both RNA and DNA (**Table 2**). Prevalence of M184V/I associated with lamivudine and emtricitabine resistance, also declined, but was higher in DNA sequences (**Table 2**).

Over the study period, prevalence of DRMs for any ARV class varied across US HHS regions. The highest DRM prevalence for RNA specimens was noted in the Northeast (HHS region 1: 34.1%) and for DNA specimens in the Midwest (HHS region 7: 37.3%) (**Figure 6A-B**).

Table 2. Prevalence of NRTI Signature DRMs

	NRTI (RNA, %)[a]		NRTI (DNA, %)	
Year	K65R/N	M184V/I	K65R/N	M184V/I
2018	1.5	11.9	1.0	19.0
2019	1.3	11.0	1.5	18.2
2020	1.1	9.7	0.9	15.3
2021	1.0	8.9	1.1	15.1
2022	0.8	8.4	0.8	13.1
2023	0.8	8.8	0.7	12.3
2024	0.7	8.6	0.8	12.5

[a]Mutations were tabulated for all sequences tested for NRTI/NNRTI/PI resistance.

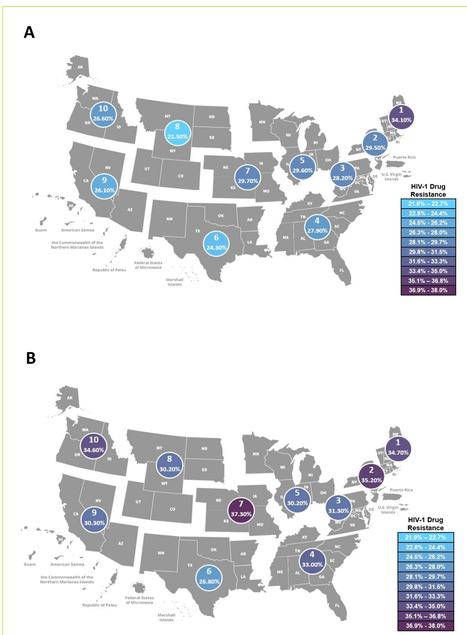


Figure 6. Prevalence of NRTI, NNRTI, PI or INSTI Resistance in the 10 US HHS Regions from 2018-2024. A: RNA sequences; B: DNA sequences

Conclusions

- Prevalence of ARV resistance among US samples submitted for commercial resistance testing has declined from 2018 to 2024.
- These trends coincided with the availability of novel regimens with enhanced effectiveness and more convenient formulations.
- Higher levels of multiclass resistance were seen in older PWH who have likely undergone longer durations of treatment with earlier generations of ARVs. This was particularly evident in the DNA testing data, which showed a greater prevalence of archived NRTI and NNRTI mutations.
- The prevalence of the integrase mutation R263K, which occurs frequently with DTG virologic failure and is associated with resistance to 2nd generation INSTIs, remains low but has increased 3-fold (0.5% to 1.5%) in RNA sequences and 2-fold (0.3% to 0.6%) in DNA sequences. This trend may impact future INSTI treatment and PrEP options.
- The K65R NRTI resistance mutation was rare and the prevalence of both K65R and M184V/I continued to decline. There is ongoing research with respect to the impact of M184V/I on contemporary lamivudine- or emtricitabine-containing regimens.[4,5]
- Doravirine, the newest NNRTI that features a non-overlapping DRM profile with 1st and 2nd generation NNRTIs, continued to exhibit a very low prevalence of resistance (2% in 2024).
- There were regional differences in ARV resistance as indicated by higher prevalences in the Northeast and Midwest, suggesting that closer surveillance of these regions is warranted.

References

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Acknowledgments

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