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Acquired HIV-1 Drug Resistance in Patients Failing an Integrase Strand Transfer Inhibitor-Based Regimen in Rhode Island, USA

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OVERVIEW

We investigated the extent, characteristics, and longitudinal trends of acquired drug resistance (ADR) to antiretroviral drugs in patients living with HIV in Rhode Island who failed treatment while on an Integrase Strand Transfer Inhibitor (INSTI)-based regimen.

BACKGROUND

- Antiretroviral therapy (ART) reduces HIV morbidity and mortality and viral transmission.
- ADR develops under selective drug pressure and remains a hurdle towards successful and sustainable treatment outcomes.
- INSTIs are now the basis for the most commonly used regimens, with five approved drugs: raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB).
- Despite minimal resistance to newer INSTI-based regimens in clinical trials, real life data on ADR upon failure of these regimens are limited. This knowledge is important for regimen design and simplification.

METHODS

- We investigated ADR upon failure of INSTI-based regimens at the largest HIV center in Rhode Island (RI), caring for >80% of the state's people with HIV.
- As part of routine drug resistance testing for clinical care, we curated a database with all available HIV sequences.
- ART histories were obtained through chart review of electronic medical records.
- Patients were included in this study if they (1) were failing an INSTI-based regimen; (2) had protease, reverse transcriptase, and integrase sequences and/or genotypic data available; and (3) had a full treatment history since the start of ART.
- Drug resistance assessments included overall, drug class, drug, and mutation-specific resistance; multi-class resistance; and resistance longitudinal trends (measured with Mann-Kendall statistics).
- Drug resistance interpretation was done with Stanford University HIV Drug Resistance Database tools (HIVdb.stanford.edu).

RESULTS

- Of 2,248 Immunology Center patients with sequences and available treatment histories, 1,169 (52%) have been on INSTI-based regimens. Of those, 185 patients (16%; with 213 eligible sequences) were failing INSTI-based regimens between 2014-2021 and fit eligibility criteria (Table1).
- INSTI breakdown of the n=185 (Figure 1): 46% on 1st-generation INSTI (38% EVG; 8% RAL), and 54% on 2nd-generation INSTI (28% BIC; 26% DTG).
- Sequences from 108/185 patients (58%) had any drug resistance, and 91/185 patients (49%; 20% on EVG, 10% DTG, 8% BIC, 7% RAL, and 5% >1 INSTI) had intermediate-high predicted resistance to any drug (see Figure 2 for common mutations; Figure 3 for drug class breakdown; Figure 4 for specific INSTI breakdown).
- Intermediate-high predicted resistance to 1st-generation INSTIs (EVG 17%, RAL 16%) was 3 times higher when compared to 2nd-generation INSTIs (CAB 6%, BIC 5%, DTG 5%) (Figure 4; 16% vs 5%).
- Resistance to 2nd-generation INSTIs was only seen in patients with prior exposure to a 1st-generation INSTI.
- Multi-class resistance was seen in 59/185 (32%) patients, 32/185 (17%) with double-, 22/185 (12%) triple-, and 5/185 (3%) quadruple-class resistance.
- Of the 27 patients with multi-class resistance to ≥3 antiretroviral classes, 14 (52%) were on a 1st-generation INSTI, 8 (30%) on a 2nd-generation INSTI, and 5 (18%) on a 1st- and 2nd-generation INSTI. There were 5 (18%) patients in this group with intermediate-high resistance to all INSTIs (see Table 2 for patient characteristics).
- Overall drug resistance significantly decreased over the examined period (Mann-Kendall statistic -0.87, 95% CI [-1,00, -0.38], p-value = 0.024) (Figure 5).

Table 1. Cohort Characteristics (n=185)

Characteristic	Estimates
Age, years (range)	38 (1-74)
Gender	69% Male, 31% Female
Race	60% White, 37% Black/African American, 1% Asian, 2% Other
Ethnicity	68% Non-Hispanic, 32% Hispanic
Time on ART, years (range)	9 (0.1-23)
Regimen Type at Failure	75% INSTI + 2NRTIs 13% INSTI + 2 NRTIs + PI 3% INSTI + PI 3% INSTI +2 NRTIs + NNRTI 6% Other

Footnote: Data on age available for all participants, on gender for 175/185, on race for 174/185, and on ethnicity for 178/185. ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Figure 1. Anchor Drug of Failed Regimen

Figure 2. Prevalence of Most Common Drug Resistance Mutations

Figure 3. Prevalence of Predicted ADR by Antiretroviral Class

Figure 4. Prevalence of Predicted ADR by INSTI

Table 2. Characteristics of Individuals with Multi-INSTI ADR

Patient	Age	Gender	Years on ART	Regimen at Failure	Viral Load at Failure, copies/mL	Drug Resistance Mutations
1	13	Male	13	EVG/c TDF FTC	15,268	L90M, M41L, M184V, T215F, Y188L, E138L, S147G, Q148R
2	20	Male	10	DTG RPV 3TC	1,080,021	M184V, K101E, S147G, N155H, Q95K
3	40	Female	9	DTG ABC 3TC	1,630	M184V, T215F, P225H, G140S, Q148H, N155H, T97A
4	42	Male	6	BIC TAF FTC	3,387	L74I, M184V, T215F, A98G, K103N, V108I, E138K, G140A, Q148R
5	45	Female	15	EVG/c TAF FTC	44,287	K70R, M184V, K219E, L100I, K103N, E138K, S147G, Q148R, T97A

Footnote: Drug resistance mutations (DRMs): protease inhibitor DRMs (red), nucleoside reverse transcriptase inhibitor DRMs (yellow), non-nucleoside reverse transcriptase inhibitor DRMs (green), integrase strand transfer inhibitor DRMs (blue).

Longitudinal Trends

Figure 5. Predicted ADR Prevalence by Year of Treatment Failure

CONCLUSIONS

- At the largest RI HIV clinic, 8% were failing INSTI-based regimens, almost half with clinically relevant drug resistance that was decreasing over time, and 3% had multi-class resistance, including few to all available INSTIs.
- Though low resistance levels to 2nd-generation INSTIs are encouraging, they exist; and continued ADR monitoring is important, particularly with increasing incorporation of INSTIs at all levels of HIV treatment and prevention, and use of 2-drug regimens.