Factors Associated with Resistance to Integrase Strand Transfer Inhibitors

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Horacio Gil[1], Elena Delgado[1], Sonia Benito[1], María Moreno-Lorenzo[1], **Michael M Thomson[1]**, and the Spanish Group for the Study of Antiretroviral Drug Resistance*.
[1]HIV Biology and Variability Unit, Centro Nacional de Microbiología, Instituto de Salud Carlos III. Majadahonda, Madrid, Spain.

BACKGROUND

The use of integrase strand transfer inhibitor (INSTI)-containing regimens in HIV-1-infected patients have experienced a global increase. Recently, WHO has emphasized the need to fast-track the transition to dolutegravir-based antiretroviral treatments. However, continued surveillance of INSTI resistance is recommended. Here, clinical, epidemiological, and virological features associated with INSTI resistance in HIV-1-infected patients attended in Spanish clinical centers were analyzed.

METHODS

Samples collected in 2008-2022 from HIV-1-infected patients attended in clinical centers from 10 Spanish regions were analyzed in integrase, protease, and reverse transcriptase using Sanger population sequencing. Antiretroviral (ARV) drug resistance was assessed with Stanford University's HIVdb program. Statistical associations were analyzed with Fisher's exact test.

- 5.8% of 3,304 HIV-1 patients (2008-2022) had INSTI resistance.
- 2.5% had resistance to 2nd generation INSTIs.
- 1.1% of 1,269 patients with new diagnoses (ND) had INSTI resistance.
- Only 2 (0.16%) NDs had resistance to DTG.
- PWID, age ≥40, and resistance to other ARV classes were associated to INSTI resistance.
- Non-subtype B viruses had lower resistance levels to RAL and EVG and less frequent resistance to DTG and BIC.

RESULTS

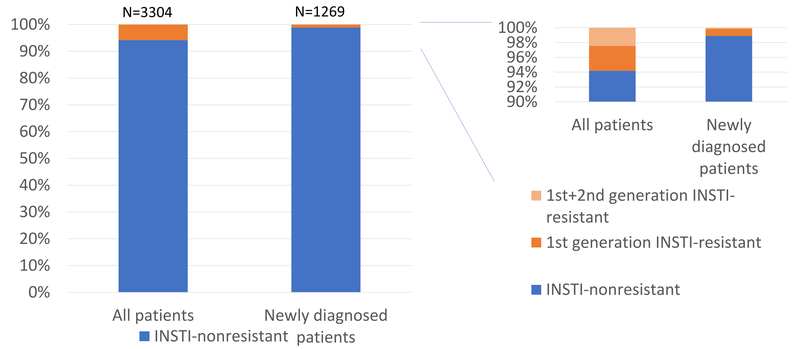

Figure 1. 5.8% of all 3,304 patients and 1.1% of 1,269 newly diagnosed (ND) patients had INSTI resistance. 2.5% of all patients and had resistance to 2nd generation INSTIs. Only 2 (0.16%) NDs had resistance to 2nd generation INSTIs, including DTG (1 low- and 1 intermediate-level).

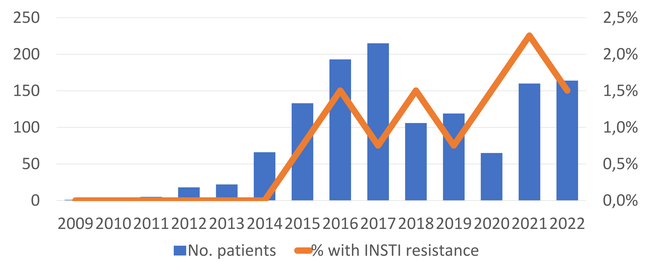

Figure 2. Among ND, low proportions of INSTI resistant viruses were maintained along time.

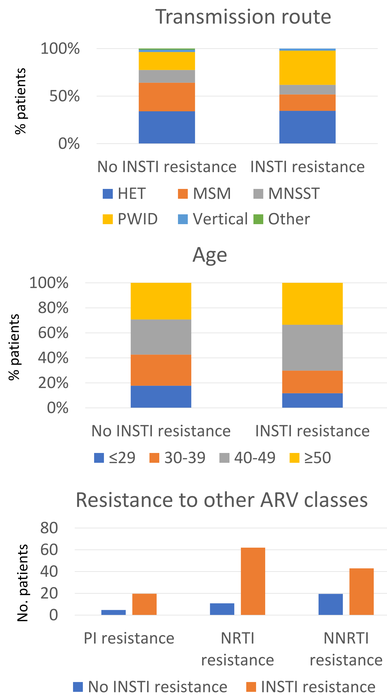

Figure 3. In univariate analysis (Fisher's exact test), INSTI resistance was significantly associated with people who inject drugs (PWID) (p<0.0001), age ≥40 (p=0.0006), and resistance to other ARV drug classes (p<0.00001).
HET: heterosexual; MSM: men who have sex with men: MNSST: men with nonspecified sexual transmission.

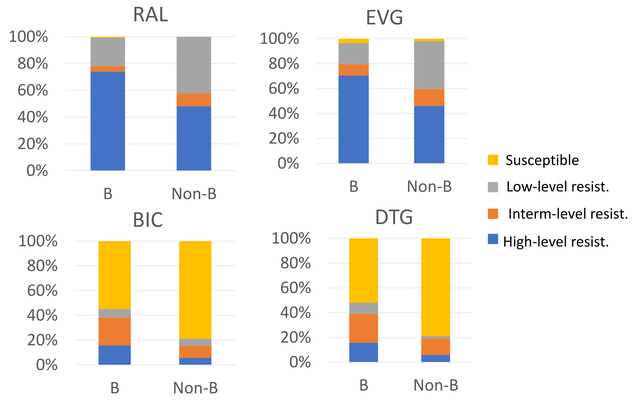

Figure 4. The frequency of INSTI resistance was similar among subtype B and non-subtype B viruses (representing 25.5% of all viruses), but among INSTI-resistant viruses, non-Bs had higher frequency of low-level resistance to RAL (p=0.0058) and EVG (p=0.0034), and lower frequency of resistance to BIC (p=0.0009) and RAL (p=0.0027).

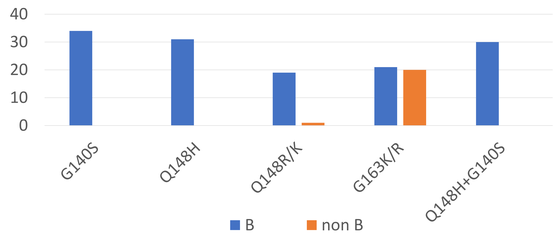

Figure 5. Non-Bs lacked G140S and Q148H resistance mutations. G163R/K was more frequent among non-Bs than among Bs (p=0.0004).

CONCLUSIONS

INSTI resistance is uncommon and associated with PWID, older age, and additional resistance to other ARV drug classes, and is rare in newly diagnosed HIV-1 infections. Lower resistance levels to RAL and EVG and less frequent resistance to DTG and BIC were observed in non-subtype B than in subtype B viruses. Our results also support the preferential use of DTG-containing regimens in first-line treatments, although surveillance of INSTI resistance is encouraged.

ADDITIONAL KEY INFORMATION

Author contact information: mthomson@isciii.es

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*The **members of the Spanish Group for the Study of Antiretroviral Drug Resistance** are listed in Gil et al. (2022) Front Microbiol 13:1051096, doi: 10.3389/fmicb.2022.1051096, where the analyses of samples collected up to May 2021 were recently published.