International Journal of Science Academic Research
Vol. 05, Issue 03, pp.7130-7132, March, 2024
Available online at http://www.scienceijsar.com

ISSN: 2582-6425

Research Article

RESISTANCE PROFILE TO INTEGRASE STRAND TRANSFER INHIBITORS IN ADULTS ROOSEVELT HOSPITAL, GUATEMALA

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Received 24th January 2024; **Accepted** 29th February 2024; **Published online** 18th March 2024

Abstract

Introducción. Integrase strand transfer inhibitors (INSTIs) are a family of antiretrovirals (ART) used for the treatment of HIV-1 infection, their mechanism of action is based on blocking the integration of proviral DNA into DNA of the host. **Objective**. To describe the resistance profile to Integrase Strand Transfer Inhibitors -INSTIs- in patients with therapeutic failure to multiple antiretroviral regimens. **Methodology**. Descriptive cross-sectional study that included 41 records of HIV-1 positive adult patients with multiple failure, who were indicated to perform a genotype test of the integrase region of the HIV-1 pol gene from February 2018 to March 2021. The analysis was carried out in the DeepChek® v2.0 software, for the classification of resistance the HIV Drug Resistance Database (HIVdb) Stanford University v9.5 algorithm (2023/08/22) was followed. **Results.** 51.2% of the patients were male. The median age at the time of requesting the test was 40 years (IQR 30, 46). 34.1% (14/41) of general resistance was identified. The highest drug resistance was found in Elvitegravir with 26.8% (11/41) followed by Raltegravir at 24.4% (10/41). The most frequently identified primary mutations were G140A/S and Q148H in 35.7% (5/14) each, as well as N155H and E138K in 21.4% (3/14) each. **Conclusion** The data presented in this study show the importance of acting promptly when suspected virological failure in patients with failure to multiple therapies, which include the use of INSTI; as well as maintaining periodic surveillance of drug resistance in both pretreated patients and those who have not been exposed to ART, which will allow trends to be identified and support the implementation of timely interventions.

Keywords: HIV-1, resistance, integrase inhibitors, Guatemala.

INTRODUCTION

Integrase strand transfer inhibitors (INSTIs) are a family of antiretrovirals (ART) used for the treatment of HIV-1 infection, their mechanism of action is based on blocking the integration of proviral DNA into DNA of the host (Gualtero, 2019). INSTIs represent a better alternative compared to the effectiveness of therapies based on non-nucleoside reverse transcriptase inhibitors (NNRTI) (OMS, 2021); However, mutations associated with the failure of first and second generation INSTI have been described (Bernal, 2016; Gualtero, 2019;Cecchini, 2019), with the latter having a greater genetic barrier (Gualtero 2019); Furthermore, mutations that confer resistance to a drug can generate cross-resistance with other ART of the same family (Bernal, 2016; Wensing, 2022;Stanford HIVdb). The emergence of HIV-1 resistance can jeopardize the effectiveness of drugs, limiting future therapeutic options (OMS, 2021;Garrido, 2008), while it could cause an increase in morbidity and mortality associated with this virus (OMS, 2021). At the Comprehensive Care Unit for HIV and Chronic Infections "Dr. Carlos Rodolfo Mejía Villatoro" of the Roosevelt Hospital, the use of INSTI was included as a therapeutic option in cases of multiple failure of nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs and protease inhibitors (PIs) families, starting in 2013, Raltegravir (RAL) was the first ART included in this family, contemplated in the National Guide for the use of ARTs in force that year (MSPAS, 2013); Subsequently, Dolutegravir (DTG) was available in 2017, Elvitegravir (EVG) in 2019 and Bictegravir (BIC) in 2022. Currently, the national guidelinesindicate the use of INSTI in the first-line regimen (MSPAS, 2019). The aim of the present investigation is to describe the resistance profile to INSTIs in patients with therapeutic failure to multiple regimens.

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MATERIALS AND METHODS

Population and sample: A descriptive cross-sectional investigation was carried out that included the records of 41 HIV-1 positive adult patients with virological failure treated at the "Dr. Carlos Rodolfo Mejía Villatoro" of the Roosevelt Hospital, who were instructed to perform a genotype test of the integrase region of the HIV-1 pol gene during the period from February 2018 to March 2021. The sampling method was non-probabilistic of consecutive cases.

Patient selection criteria

- Present at least two HIV-1 viral loads in plasma >1000 copies/mL within a period of 4 to 12 weeks apart.
- Documented resistance to at least one family of first or second line ART (NRTIs, NNRTIs or PIs).
- Documented record of INSTI use.

Genotyping of the integrase region of the HIV-1 *pol* gene: Sequencing was performed on the MiniSeq™ - Illumina system, using DeepChek® v2.0 software. For the classification

of resistance, the HIV Drug Resistance Database (HIVdb) Stanford University v9.5 (2023/08/22) algorithm was followed, both the score and its interpretation were used. Resistance levels were grouped into 3 categories for each drug: Possible/low level of resistance corresponds to Stanford score (SS) of 10-29, intermediate level of resistance to SS of 30-59 and high level of resistance to SS ≥ 60. Internationally recognized mutations were analyzed.

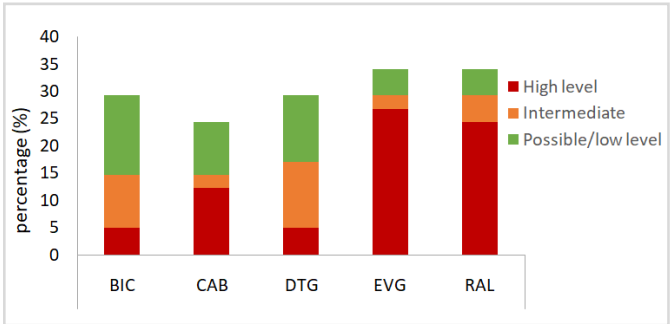
Data collection instrument and procedure: The database was generated in an Excel Office 2019 electronic sheet. The information was tabulated in the pre-established order of the fields. From the database of the sequencing area of the laboratory of the Comprehensive Care Unit for HIV and Chronic Infections "Dr. Carlos Rodolfo Mejía Villatoro" of the Roosevelt Hospital, the variables sex, age and department of residence were obtained. Resistance and mutation profiles were transcribed from the Stanford database (v9.5 – 2023/08/22).

Analysis of data: It was carried out using the freely distributed statistical software Jamovi v2.3.26. The patients characteristics are described through frequencies and percentages, the quantitative variable in median and inter quartile range. The prevalence of resistance is presented in 95% confidence intervals. To determine the association between the presence of resistance and the characteristics studied, the Chi-2 test was used, with a significance level of 0.05. Resistance profiles and mutations were analyzed in percentages.

Ethical aspects: The request for informed consent for participants did not apply because during the research there was no intervention for patients. No identifying information was included to maintain patient confidentiality. The research protocol was reviewed and approved by the authorities of the Department of Internal Medicine, Comprehensive Care Unit for HIV and Chronic Infections "Dr. Carlos Rodolfo Mejía Villatoro" of the Roosevelt Hospital and by the Department of Teaching and Research of the same hospital.

RESULTS

The INSTI resistance test was performed on 41 patients with documented multiple failure to ART, 51.2% were male. The median age at the time of requesting the test was 40 years (IQR 30, 46). 34.1% (14/41) of general resistance was identified. The highest drug resistance was found in EVG with 26.8% (11/41) followed by RAL in 24.4% (10/41). The most frequently major mutations identified were G140A/S and Q148H at 35.7% (5/41) each.



BIC: bictegravir, CAB: cabotegravir, DTG: doultegravir, EVG: elvitegravir, RAL: raltegravir

Figure 1. Resistance profile of integrasestrand transfer inhibitors

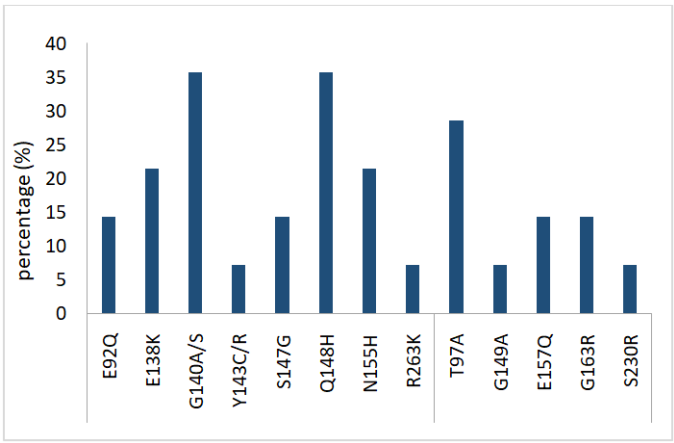


Figure 2. Mutations associated with integrasestrand transfer inhibitors

DISCUSSION

During the years covered by this study, the use of INSTI was restricted to patients with failure to multiple ART regimens, later it was integrated for use in cases considered special such as pregnancy and intolerance to other ARVs and currently this family of drugs is part of first-line of antiretroviral therapy. In the present study, general resistance to INSTIs was found in 34.1% (14/41) of the cases analyzed. Expectedly, a high level of resistance is observed to RAL and EVG (figure 1), since they are drugs from the first-generation INSTI family that generate resistance relatively quickly and are frequently associated with cross-resistance between them (GeSIDA, 2018), unlike BIC and DTG [4.9% (2/41)] which are second generation and have a greater genetic barrier (Gualtero, 2019) so resistance will be lower. However, it is considered that if a patient maintains a low genetic barrier ART for a long time, in the presence of virological failure such as RAL and EVG, it could also negatively affect the efficacy of other ART from the same family (Zhang, 2018). Regarding the major mutations associated with the use of INSTI, the most frequent were the non-polymorphic mutations G140A/S and Q148H (35.7% each) (figure 2), which generally occur in combination and are associated with the use of RAL and EVG (Garrido, 2008).In addition, they can also reduce the susceptibility of BIC, DTG and cabotegravir (CAB) due to the high cross-resistance between both RAL and EVG, as well as these with the other INSTIs (Zhang, 2018; Stanford HIVdb; Wensing, 2022).

The non-polymorphic mutations N155H and E138K (21.4% each) were also found, associated mainly with the use of RAL and EVG, but also with the other INSTIs (Gualtero, 2019; Stanford HIVdb); the N155H mutation alone decreases susceptibility to RAL and EVG approximately 10 and 30-fold, respectively, but has minimal effect on susceptibility to BIC, DTG, and CAB. On the other hand, the E138K mutation alone does not reduce susceptibility to INSTIs; however, combined with other mutations, mainly those at position 148, they reduce susceptibility to the ARTs of this family (Stanford HIVdb). Resistance to INSTIs in pretreated patients analyzed in this study has been reported by other authors in different proportions (figure 1): in Spain, 6.5% (174/2,696) of patients registered in a database from 2008 to 2021 presented resistance to first-generation INSTI and 2.6% (71/2,696) also had resistance to second-generation INSTI (Gil, 2022); In a multicenter study carried out in France, 53.3% (359/674) presented resistance to RAL, 22.8% (154/674) to EVG and

23.9% to DTG (Marcelin, 2019); Likewise, the predominant primary mutations in this study were also identified in a cohort of 67 patients treated in two public health institutions and one private health institution located in Buenos Aires, Argentina, in which 94% were receiving RAL and 71.9 % had INSTI resistance mutations: N155H (35.1%), Q148H/R (15.8%) and G140A/S (14%) (Cecchini, 2019). Regarding the most frequent accessory mutations (Figure 2), the polymorphic T97A mutation (28.6%) can appear between 1 and 5% of people not treated with drugs from this family. Its presence alone has minimal effects on susceptibility to INSTIs, but in combination with other important resistance mutations, it synergistically reduces susceptibility to each of the INSTIs. (Stanford HIVdb; GeSida, 2018). In the Comprehensive Care Unit for HIV and Chronic Infections at the Roosevelt Hospital, the RAL has been used more than any other INSTIs, therefore greater resistance to the first-generation drugs of this family was to be expected in the patients included in this study, due to the time of use and for the cross resistance between RAL and EVG; However, the higher level of resistance identified in the EVG could be due to the fact that in some patients the use of RAL was extended in the presence of virological failure because the lack of pharmacological options, which caused the accumulation of mutations that are associated with cross-resistance in both ARTs; In addition, the presence of mutations associated with the use of RAL and/or EVG could contribute to the development of significant resistance to BIC and DTG that entered the country long after the first generation INSTI even though these patients have not been exposed to second-generation INSTI.

It is important to mention that during the period analyzed more than 90% of the patient cohort remained in virological suppression with the first and second line treatment regimens (NRTI, NNRTI and IP) of which were available at that time, leading to four important considerations in relation to the use of INSTI: 1) suspicion and confirmation of virological failure, 2) addressing adherence to ART, 3) availability of resistance testing, 4) access to optimal drugs. The persistence of virological failure is caused mainly by lack of treatment adherence and also by supply shortage of RAL and EVG in the past, those could be favorable factors for the accumulation of mutations, potentially negatively affecting the efficacy of the second generation INSTI, due to cross resistance, especially for CAB [12.2% (5/41)], an INSTI that has not been used in the country so far. This would have important implications at the pharmacological if CAB were available, it would be necessary to carry out a resistance test in patients with prior use of this ART family before starting this drug. In addition, an optimal drug combination should be considered in the presence of associated mutations in patients with limited treatment options due to multiple failures.

CONCLUSION

The data presented in this study demonstrate the importance of acting promptly upon suspicion of virologic failure in patients with multiple therapy failures that include the use of INSTI, such as confirming the failure, addressing adherence to ART and performing resistance testing to guide the selection of optimal drugs. In addition, our results highlight the need to maintain periodic surveillance of drug resistance with special attention to both INSTI-pretreated and ART-naive patients, which will allow us to identify trends and support timely interventions.

Acknowledgments

To the team at the Comprehensive Care Unit for HIV and Chronic Infections, Roosevelt Hospital, especially Julio Paxtor, Regina Reynoso and Diana Baldizón for their contribution to the development of the study.

Conflict of interests: The authors declare that they have no conflict of interest.

Financing sources: This study was not funded.

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