SAGE Open Medical Case Reports
Volume 11: 1–3

DOI: 10.1177/2050313X231220786
journals.sagepub.com/home/sco
Sage

Development of *H51Y* and *E157Q* mutations for integrase inhibitor resistance in a patient undergoing treatment for pulmonary tuberculosis: A case report

Luís Arthur Brasil Gadelha Farias[1,2], Melissa Fiuza Saboya[3], Natália Ponte Fernandes[3], Lauro Vieira Perdigão Neto[1,2] and Erico Antonio Gomes de Arruda[1,3,4]

Abstract

Background: Failure of first-line regimens with dolutegravir, a high genetic barrier antiretroviral of the integrase inhibitor class, although uncommon, tends to increase in prevalence due to broader use.

Objective: To describe the clinical case of an HIV/Tuberculosis coinfected patient who developed Human Immunodeficieny Virus (HIV) treatment failure during dolutegravir therapy.

Case report: Male, 29 years old, presented with a right cervical mass, dry cough, and hyporexia, which lasted 2 weeks. Diagnostic tests were positive for tuberculosis and HIV. The viral load was 437,927 cp/mL (Log = 5.64). Antiretroviral therapy was initiated with Tenofovir/Lamivudine and Dolutegravir (TDF/3TC and DTG), the latter at a dose of 50 mg/day, as was a regimen for tuberculosis. After 8 months, therapeutic failure was verified. Genotyping was requested, with detection of the *H51Y* and *E157Q* mutations in the integrase.

Conclusion: Attention when determining the antiretroviral therapy treatment regimen of HIV/TB coinfected patients is paramount. Poor adherence to antiretroviral therapy and follow-up may have contributed to treatment failure and resistance.

Keywords

HIV/AIDS, integrase inhibitor, tuberculosis, ART

Date received: 4 June 2023; accepted: 23 November 2023

Introduction

Antiretrovirals promote the control of HIV replication, thus increasing the survival of patients living with HIV. Recently, the use of integrase inhibitors (INIs) in HIV infection has provided rapid suppression of replication, with the advantage of easier posology. Virus mutations that confer resistance to INI are rare and imply in difficult therapeutic management.[1,2] We aim to report the clinical case of a tuberculosis-HIV (TB-HIV) coinfected patient who developed HIV treatment failure during (dolutegravir) DTG therapy. This case was approved by the Research Ethics Committee of the São José Hospital of Infectious Diseases (HSJ) (CAAE: 61660022.0.0000.5044).

Case report

A 29-year-old male patient was admitted with a right cervical mass associated with fever, dry cough, hyporexia, and myalgia for more than 2 weeks, as well as neurological symptoms of headache and sudden hemiparesis. A chest examination revealed bilateral crepitations, rhonchi, and wheezes. No other findings were noted during the physical examination. Cervical ultrasonography detected a large tumoral mass with ipsilateral adenomegaly. Computed tomography of the chest showed findings consistent with miliary TB or histoplasmosis. The MTB-RIF (GeneXpert® Cepheid) and the rapid test for HIV were both positive. The baseline viral load (VL) was 437,927 cp/mL (Log = 5.64). A

[1]São José Hospital of Infectious Diseases of the Secretary of Health of the State of Ceará, Fortaleza, Ceará, Brazil
[2]University of São Paulo, São Paulo, Brazil
[3]State University of Ceará, Fortaleza, Ceará, Brazil
[4]Fortaleza University, Fortaleza, Ceará, Brazil

Corresponding Author:
Luís Arthur Brasil Gadelha Farias, Hospital São José de Doenças Infecciosas, Rua Nestor Barbosa, 315, Fortaleza, Ceará 60455-610, Brazil.
Email: luisarthurbrasilk@hotmail.com

therapeutic regimen for TB (Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol), ART (TDF/3TC/DTG), the latter at a conventional dose of 50 mg/day, and empirical therapy against histoplasmosis were initiated. A reduction of the cervical lesion and control of the neurological and systemic symptoms were observed, and the patient was discharged for further outpatient follow-up. In the next year, he returned to the outpatient clinic having used ART for 7 months, in addition to treatment for TB and histoplasmosis, reporting vomiting, nausea, hyporexia, and paresthesias, with a VL = 12,182 cp/mL (Log = 4.08). He had poor adherence to ART and did not fulfill all prescriptions. He also failed to attend medical appointments and had challenging clinical follow-up. ART was switched to TDF/3TC/EFZ, and genotyping was requested, which revealed *H51Y* and *E157Q* mutations, which are associated with resistance to INIs, including DTG, and *K70E* and *M184V* mutations in the reverse transcriptase genes. The patient was then treated with a rescue regimen of TDF/3TC/DRV600 mg/RTV100 mg, reaching a VL less than 40 cp/mL, 6 months later.

Discussion

Mutations following the use of first-line regimens with DTG, an antiretroviral drug with a high genetic barrier to resistance, are rare and clinically challenging to manage. The leading mutations related to the use of DTG were *R263K* and *G118R*, with *H51Y* and *E157Q* generally representing secondary mutations.[1] The addition of the *H51Y* mutation has been shown to cause a further drop-in viral fitness below that conferred by *R263K* alone.[2] *E157Q* represents a rare mutation found in approximately 2.4% of untreated patients.[3] In a case report, a patient with an isolated *E157Q* mutation presented failure to a regimen using and, subsequently, DTG.[4] In Brazil, TB-HIV coinfection is extremely prevalent. Rifampicin, which consists of a rifamycin with fundamental bactericidal action for the treatment of TB, interacts with DTG by inducing the liver enzymes *UGT1A1* and *CYP3A*, thus reducing the plasma concentrations of this drug.[5] The use of DTG, without adjustment, as well as protease inhibitor/ritonavir (PI/r) with rifampicin, may pose risks to the virological control of these patients, including the possibility of viral resistance.

On the other hand, a recent clinical trial comparing once-daily DTG with TB treatment rather than twice-daily DTG in the same situation has seemed effective in patients with TB-HIV coinfection.[6] The Rifampicin and Dolutegravir Investigation of Novel Treatment dosing in Tuberculosis (RADIANT-TB) was a double-blind study and enrolled 108 individuals disposed as once-daily DTG ($n = 55$) and twice-daily DTG ($n = 53$). No resistance was identified after 19 months related to INI. His findings suggested that twice-daily dolutegravir might be unnecessary in people with HIV-associated tuberculosis.[6]

In the present case report, the pharmacokinetic interaction between rifampicin and DTG, which was used at a low dose (50 mg/day), may have contributed to subinhibitory tissue levels and the emergence of resistance mutations. Another important aspect was the patient's poor adherence and absence of correct follow-up, which could have also contributed to the emergence of INI mutations in this case. Close attention must be paid regarding the antiretroviral treatment of patients coinfected with TB to avoid dosage inadequacies that could impair the therapeutic response. Despite the absence of mutations identified in single-dose DTG clinical trials,[6] this case report may emphasize the importance of continued vigilance for mutations in TB-HIV coinfected patients receiving single-dose DTG.

Conclusion

Documented cases of emergent INI resistance mutations against first-line DTG are rare. Drug interactions, as well as poor adherence and absence of follow-up, may contribute to the emergence of INI mutations. More studies are necessary to understand the safety and efficacy of once-daily DTG in patients undergoing rifampicin treatment for tuberculosis.

Acknowledgements

The authors would like to acknowledge all the residents and staff of the Hospital São José de Doenças Infecciosas (HSJ) in Fortaleza, Brazil, for their valuable support.

Authors' contribution

L.A.B.G.F.: Conception, writing and approved the final article. M.F.S. and N.P.F.: Conception, and writing. L.V.P.N., E.A.G.A., and L.A.B.G.F: Supervision, and critical review of the article and approved the final article.

Data availability

Information regarding this case is available upon request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Ethical approval to report this case was obtained from Committee of the São José Hospital of Infectious Diseases (HSJ) (CAAE: 61660022.0.0000.5044; Protocol Number: 5.838.398).

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article. The authorized informed consent was obtained after the clinical resolution of neurological symptoms during the follow-up after hospitalization.

ORCID iD

Luís Arthur Brasil Gadelha Farias https://orcid.org/0000-0002-8978-9903

References

1. Anstett K, Brenner B, Mesplede T, et al. HIV drug resistance against strand transfer integrase inhibitors. *Retrovirology* 2017; 14(1): 36.
2. Quashie PK, Oliviera M, Veres T, et al. Differential effects of the *G118R, H51Y*, and *E138K* resistance substitutions in different subtypes of HIV integrase. *J Virol* 2015; 89(6): 3163–3175.
3. Charpentier C and Descamps D. Resistance to HIV integrase inhibitors: about *R263K* and *E157Q* mutations. *Viruses* 2018; 10(1): 41.
4. Ambrosioni J, Nicolás D, Manzardo C, et al. Integrase strand-transfer inhibitor polymorphic and accessory resistance substitutions in patients with acute/recent HIV infection. *J Antimicrob Chemother* 2017; 72(1): 205–209.
5. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defsic Syndr* 2013; 62(1): 21–27.
6. Griesel R, Zhao Y, Simmons B, et al. Standard-dose versus double-dose dolutegravir in HIV-associated tuberculosis in South Africa (RADIANT-TB): a phase 2, non-comparative, randomised controlled trial. *Lancet HIV* 2023; 10(7): e433–e441.