Implications and considerations of V179D mutation in a patient with HIV treated with cabotegravir/rilpivirine: A case report and mini-review of the literature

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Received December 29, 2023; Accepted February 27, 2024

DOI: 10.3892/wasj.2024.234

Abstract. The management of antiretroviral therapy is intricately associated with the evaluation of the viral genetic profile, a process in which infectious disease specialists play a pivotal role in both the selection and fine-tuning of treatment protocols. The V179D aminoacidic variation within the reverse transcriptase of the human immunodeficiency virus (HIV), while not considered among major mutations, carries the potential to exert a notable effect on resistance to antiretroviral agents. Notably, this influence extends specifically to the class of non-nucleoside reverse transcriptase inhibitors, suggesting that the presence of the V179D mutation may diminish the susceptibility of the virus to certain antiretroviral drugs within this classification. The present study describes the case of a patient which delineates the management trajectory of an HIV-positive individual, commencing from the initial diagnosis in November, 2017. A genotypic resistance test revealed the presence of the V179D mutation. Of note, notwithstanding the existence of this mutation, the patient underwent a transition to a cabotegravir and rilpivirine injectable combination regimen, resulting in a favorable treatment response characterized by comprehensive and sustained viral suppression, coupled with enhancements in the immunological profile. The case described herein underscores the critical significance of a tailored approach in the management of HIV, wherein therapeutic strategies are adeptly tailored to the unique exigencies of people living with HIV.

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Key words: human immunodeficiency virus, non-nucleoside reverse transcriptase inhibitor, resistance mutations, V179D

Introduction

Human immunodeficiency virus (HIV) is known for its ability to mutate rapidly, which significantly affects how it responds to antiretroviral therapy and the progression of the disease (1). Effectively managing these mutations is a crucial aspect of antiretroviral therapy. The early detection of drug-resistant mutations is key to customizing treatment to provide optimal outcomes and avoiding cumbersome complications (2-4).

Mutations in HIV refer to changes in its genetic makeup that can affect several factors, such as replication, drug resistance and the ability to avoid the immune system, making it more difficult to control the infection (1,2,5). Often, major mutations linked to drug resistance develop due to prolonged drug exposure (6). These resistance mutations can appear in parts of the genome responsible for producing proteins that are essential for the lifecycle of the virus, such as reverse transcriptase, protease and integrase, reducing the effectiveness of certain antiretroviral drugs (2). Mutations can also occur in the long terminal repeat regulatory regions or affect the tropism of the virus, namely its ability to infect specific cell types, such as cells with CCR5 or CXCR4 receptors, which can alter the progression of the disease (5-12).

Among these mutations, the V179D mutation has emerged as a focal point due to its association with resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), a cornerstone in the treatment of HIV-1 (13). Recent studies have underscored the prevalence and impact of the V179D mutation, illuminating its role in complicating antiretroviral therapy (ART) regimens (13,14).

In Shanghai, China, an ambispective cohort study (13) shed light on the prevalence and influence of the V179D mutation among ART-naïve patients. This mutation was identified in a significant proportion of patients, influencing their virological response to first-line efavirenz-based regimens. It was observed that such regimens may be less effective for patients harboring the V179D mutation, particularly in those presenting with high baseline viral loads (VLs) (13). This finding is critical, as it

suggests the necessity for tailored treatment approaches in patients with this specific mutation.

Additionally, a previous study focusing on HIV-1 CRF65_cpx strains revealed the natural presence of the V179D mutation, alongside the K103R/V179D combination (14). The findings of that study contribute to the understanding of the genetic diversity of HIV-1 and the complexities surrounding drug resistance. The findings also highlight the importance of recognizing the variability of HIV-1 subtypes and their respective resistance patterns, which are pivotal in guiding effective treatment strategies (14).

Handling drug resistance requires the detailed genetic analysis of the virus and adapting ART to the unique resistance profile of each patient (6). The field of understanding HIV mutations is constantly evolving, with the genetic diversity of the virus presenting a significant challenge in treating infections. Ongoing research is essential to keep track of HIV mutations and develop novel treatment methods (2,5-10,12).

The present study describes the case of a patient diagnosed with HIV-1, found to have the V179D mutation. The present case report delves into the treatment journey of the patient, examining the implications of this mutation on his response to standard ART. By drawing on the insight from recent studies and the clinical trajectory of the patient, the present case report aimed to elucidate the challenges and clinical decision-making processes in the management of patients with HIV-1 with the V179D mutation. In this manner, the authors aim to contribute to the broader discourse on personalized HIV treatment strategies and the management of drug-resistant HIV variants.

Case report

The present study describes the case of a 37-year-old Caucasian male living with HIV who is being treated at the Infectious Diseases Unit at the 'ARNAS Garibaldi Nesima' Hospital (Catania, Italy). This patient was diagnosed with HIV in November, 2017. The patient is a MSM (men who have sex with men) and does not have any other comorbidities, apart from anal condylomatosis related to human papillomavirus. The patient stated that he smoked 20 cigarettes a day, denied alcohol use, and stated that he used cannabis for medicinal purposes. Hepatitis B virus, hepatitis C virus, VDRL/TPHA serological tests yielded negative results.

Initially, the patient exhibited 38,764 copies/ml of HIV-RNA, 17% $CD4^+$ T-cells, 81% $CD8^+$ T-cells, and a CD4/CD8 ratio of 0.22 (Table I). ART was promptly administered, using a single-tablet combination of dolutegravir (DTG) at 50 mg/die, and abacavir (ABC) and lamivudine (3TC) at 600/300 mg/die.

In addition, a genotypic resistance test (ViroSeq™ HIV-1 Genotyping System, Thermo Fisher Scientific, Inc.) was performed to identify any mutations in HIV that may lead to antiretroviral drug resistance. The results revealed a low potential resistance to NNRTIs, particularly due to the V179D mutation. No other major or minor resistance was detected. HLA-B5701 was not detected.

At 1 month after commencing ART, the VL of the patient markedly decreased to 108 copies/ml, and by February, 2018, it decreased to <20 copies/ml. The immunological panel

Table I. The viro-immunological trend of the patient over time.

		Administration of dolutegravir/lamivudine/abacavir over time (month/year)						Adminstration of dolutegravir/ lamivudine over time (month/year)				Administration of rilpivirine/ cabotegravir (LA) over time (month/year)			
Parameter	12/2017	01/2018	02/2018	08/2018	01/2019	07/2019	07/2020	04/2021	07/2021	01/2022	07/2022	01/2023	03/2023	06/2023	08/2023
$CD4^+$, %	17	18	22	27	22	21	21	22	23	21	22	22	22	22	24
$CD4^+$, cells/mmc	335	275	423	397	739	809	633	1027	977	929	1089	916	1047	864	882
$CD8^+$, %	81	75	76	65	56	54	53	52	50	53	47	50	48	41	50
$CD8^+$, cells/mmc	1,546	1,132	1,404	932	1,857	2,053	1,599	2,406	2,068	2,355	2,316	2,048	2,197	1,689	1,809
CD4/CD8 ratio	0.22	0.24	0.30	0.43	0.40	0.39	0.40	0.43	0.47	0.39	0.47	0.45	0.48	0.51	0.49
HIV-RNA, copies/mmc	38,764	108	<20	<20	21	<20	U	U	35	<20	U	U	U	U	U

The U, undetectable; LA, long-acting.

Table II. Major non-nucleoside reverse transcriptase inhibitor resistance mutations.

Mutation	High-level reduced susceptibility or virological response	Reduced susceptibility or virological response	Reduced susceptibility in combination with other NNRTI-resistance mutations
L100I	ETR/RPV	EFV/NPV	DOR
F227C		ETR/RPV	
K101E			DOR
K101EP	NVP	EFV/ETR/RPV	
K103NS	EFV/NVP		
V106AM	NVP	DOR/EFV	
Y181IV			DOR
Y181CIV	NVP	ETR/RPV	EFV
Y188L	DOR/EFV/RPV/NVP		ETR
G190SE		DOR	
G190ASE	NVP	EFV/ETR/RPV	
F227LC	DOR	EFV/NVP	
M230L	DOR/EFV/NVP	ETR/RPV	

ETR, etravirine; RPV, rilpivirine; EFV, efavirenz; DOR, doravirine; NVP, nevirapine.

of the patient also improved: The number of $CD4^+$ cells increased to 22%, that of $CD8^+$ cells decreased to 76%, and the CD4/CD8 ratio increased to 0.30. The patient did not report any side-effects, demonstrating a good compliance.

In June, 2021, the treatment was simplified to a two-drug regimen including DTG at 50 mg/die and 3TC at 300 mg/die (single tablets), removing ABC to reduce toxicity and related comorbidities. This change maintained viral suppression through 2022, with the HIV-RNA of the patient becoming undetectable, the number of $CD4^+$ cells stabilizing at 22%, that of $CD8^+$ reducing to 50%, and the CD4/CD8 ratio improving to 0.45.

In February, 2023, the patient exhibited interest in switching to injectable long-acting (LA) therapy, administered intramuscularly every 2 months. This included a combination of cabotegravir at 600 mg and rilpivirine (RPV) at 900 mg, designed to simplify treatment and improve the quality of life.

Despite V179D mutation, the patient responded well to the RPV-containing LA regimen. By March 28, 2023, the patient maintained an undetectable HIV-RNA level, with 22% $CD4^+$ (1,047 cells/mmc), 48% $CD8^+$ (2,197 cells/mmc) and a CD4/CD8 ratio of 0.48. Further analysis in August, 2023 confirmed the success of this therapy: Undetectable HIV-RNA, 24% $CD4^+$ T-cells (882 cells/mmc), 50% $CD8^+$ T-cells (1,809 cells/mmc) and a CD4/CD8 ratio of 0.49 (Table I). To date, the patient has successfully maintained viral suppression and continues to exhibit gradual, yet consistent immunological improvement.

Discussion

The genetic diversity of HIV-1 is a pivotal factor in the evolution of drug resistance, a phenomenon intricately associated with geographical variations and patient demographics (1,2). This diversity is influenced, not only by the range of mutations, including major and minor ones, but also by regional HIV subtypes and socio-economic conditions. In regions such as sub-Saharan Africa, where subtype C of HIV-1 is prevalent, the mutation patterns and resistance profiles differ significantly from those in Western countries, where subtype B is more common. These disparities highlight the need for region-specific HIV treatment guidelines and strategies (1,2).

Mutations in HIV-1, categorized as either major or minor based on their impact on viral replication and drug sensitivity, emerge primarily due to the error-prone nature of the reverse transcriptase enzyme (2). This enzyme lacks a proofreading mechanism, leading to frequent errors during viral replication. The rapid replication rate of HIV, coupled with the selective pressure of antiretroviral drugs, further accelerates the development of resistant strains.

Major mutations in the reverse transcriptase enzyme, such as M184V/I, K65R and Q151M confer resistance to nucleoside reverse transcriptase inhibitors (NRTIs), affecting the efficacy of drugs such as lamivudine and emtricitabine. Similarly, NNRTI resistance is often due to mutations, such as L100I, Y188L and M230L in the reverse transcriptase, affecting drugs such as doravirine, efavirenz and etravirine (6,8,11,12).

In the protease enzyme, mutations such as V32I and I84V are known for causing resistance against protease inhibitors, such as atazanavir, darunavir and lopinavir. Furthermore, mutations in Gp41 and Gp120 influence the sensitivity of the virus to fusion inhibitors and CCR5 inhibitors, respectively (15).

The integrase enzyme is also subject to mutations that can confer resistance to integrase strand transfer inhibitors (9,11,12). The implications of HIV resistance in terms of NNRTI susceptibility are summarized in Table II.

A key distinction in drug resistance mutations is between polymorphic mutations, which occur naturally, and non-polymorphic mutations, which develop in response to therapy (14).

A common polymorphic mutation is V179D in the reverse transcriptase enzyme, associated with potential low-level resistance to NNRTIs. Although typically categorized as a minor mutation, the impact of V179D can vary based on the presence of other mutations, such as K103R, which can significantly reduce susceptibility to NNRTIs (15).

Recent studies, including one conducted in Shanghai, China, investigated the prevalence of the V179D/E mutation in patients with ART-naïve HIV (13). That study demonstrated a high prevalence of the mutation, which was associated with poorer responses to efavirenz-based regimens, particularly in patients with high baseline VL (13). These findings underscore the importance of considering VL and resistance patterns at the onset of therapy (16).

The advancement of technologies such as next-generation sequencing has been instrumental in detecting low-frequency mutations and guiding treatment modifications (17). This precision is critical in managing HIV effectively and underscores the complexity of the genetic landscape of the virus (18). Furthermore, the role of co-infections, such as tuberculosis or hepatitis C virus, has been recognized in altering mutation rates and patterns in HIV, necessitating tailored treatment approaches (19-21). Additionally, the field of pharmacogenomics is unveiling how individual genetic differences can influence drug metabolism, paving the way for personalized HIV therapies (22).

In a clinical context, flexible and personalized treatment approaches are key. The case reported herein demonstrated that a patient with the minor V179D mutation responded well to a LA injectable regimen containing RPV, highlighting the effectiveness of that therapy even in presence of minor resistance for NNRTI and the importance of adaptability in treatment strategies (23). This approach, coupled with an understanding of the psychosocial factors affecting adherence, can significantly improve the quality of life and clinical outcomes of patients (24).

The management of HIV drug resistance also has broad implications for public health policies. Effective monitoring, reporting systems and global collaborations are crucial in understanding and managing resistance patterns. Policies promoting access to testing, treatment and prevention services are fundamental in addressing the global HIV epidemic (25).

The dynamic nature of HIV-1 and its drug resistance patterns demands continuous research and adaptation in treatment strategies. Understanding the interplay of mutations, the influence of regional and individual factors, and the advancements in technology and pharmacogenomics are essential in the effective management of HIV infection worldwide.

In conclusion, the present study reports the case of a patient with HIV-1 and highlights the critical need to recognize that HIV-1 mutations and consequent drug resistance vary among individuals, necessitating personalized assessments of viral resistance. The management of HIV infection must be customized to the specific genetic profile of the virus in each patient. The case discussed herein epitomizes the importance of individualized management in HIV care, adapting therapy to meet the needs and preferences of the patient. This approach is crucial, not only for increasing compliance, but also for significantly improving the quality of life and the psychological well-being of people living with HIV. Since diagnosis, the patient has demonstrated significant viro-immunological progress across various therapeutic phases. Despite the presence of the minor V179D mutation, which could potentially affect the response to injectable therapy containing RPV, the patient exhibited a positive response to this new regimen. Although the present study reports the case of a single patient and the results should not be generalized without performing larger studies, this success underscores the benefits of less frequent administration via monthly intramuscular injections, thereby enhancing adherence.

The findings of the present study emphasize that the impact of specific mutations, such as V179D can vary, depending on several factors, including the overall genetic makeup of the virus and the presence of other, particularly major, mutations. This case reinforces the need for continuous monitoring and active collaboration between the patient and the medical team to ensure long-term success in managing HIV infection. Furthermore, the discussion underlines the importance of acknowledging global variations in HIV-1 mutations, advancements in mutation detection technology, and the role of pharmacogenomics in optimizing treatment strategies. These aspects collectively lead to a more effective and personalized approach in combating HIV/AIDS.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' contributions

All authors (SS, AM, BMC, EVR, FC, BC and GN) contributed to the study conception and design. SS and AM were conceptualized the study. BMC, EVR and FC were involved in analyzing and treating the patient, and in writing, reviewing and editing the manuscript. SS, AM and BMC were involved in analyzing/treating the patient. SS and AM were involved in the writing and preparation of the original draft. GN and BC supervised the study. GN and BC confirm the authenticity of all the raw data. All authors have read and agreed to the published version of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from the patient whose case is depicted in the present study.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the present case report.

Competing interests

The authors declare that they have no competing interests.

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