Case Report

The Challenge of Adherence to a Complex Antiretroviral Therapy Regimen in an Individual With Multidrug-Resistant HIV

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Abstract: *Limited therapeutic options are available for patients with multidrug-resistant HIV. This report describes a 38-year-old female who was perinatally infected with HIV-1 and treated with 14 different antiretroviral regimens over 27 years, gradually leading to 4-class drug resistance. Despite various attempts to obtain sustained viral suppression, including the off-label administration of intravenous foscarnet and enfuvirtide, and thorough follow-up with 16 viral genotyping/phenotyping from 1999 to 2021, viral control was not maintained. Recently, the introduction of a regimen with fostemsavir and lenacapavir resulted in long-term viral suppression.*

Keywords: HIV, AIDS, multidrug resistance, integrase strand transfer inhibitor, resistance, foscarnet, fostemsavir, lenacapavir

Introduction

The number of people who are living with HIV and receiving antiretroviral therapy (ART) is increasing worldwide. Incomplete viral suppression because of low adherence or suboptimal ART leads to the emergence of HIV resistance-associated mutations. The most affected classes are nucleoside reverse transcriptase inhibitors (nRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs).[1-5] Epidemiologic studies in high-income countries, including Belgium, reported a prevalence of 2.4% to 10% in baseline resistance to at least 1 drug in each of the nRTI, NNRTI, and protease inhibitor (PI) classes.[4,5] Resistance-associated mutations to the first-generation integrase strand transfer inhibitors (InSTIs), raltegravir (RAL) and elvitegravir (EVG), were reported in fewer than 1% of drug-naive patients with HIV in Belgium.[5] Acquired triple-class drug resistance seems to be more common in patients who acquired HIV perinatally, especially if treatment adherence issues are observed. Moreover, delay before starting ART is often longer in patients with perinatal HIV.[4]

Fostemsavir (FTR) is a first-in-class attachment inhibitor that binds to glycoprotein 120 in the viral envelope. Preliminary results of a phase III study showed complete viral suppression at week 48 in 54% of the individuals with multidrug-resistant HIV and randomly assigned to FTR combined with optimized background therapy.[6] Lenacapavir (LEN) is a first-in-class inhibitor of the HIV-1 capsid, and its in vitro and in vivo activity is maintained against viruses harboring mutations responsible for resistance to nRTIs, NNRTIs, PIs, and InSTIs.[7,8]

Few reports describe the treatment for patients with multidrug-resistant HIV.[9-11] Rescue strategies include anti-CD4 monoclonal antibody therapy and immunoglobulin administration combined with ART. Other studies evaluated foscarnet (FNT) administration for rescue therapy.[12,13] Nevertheless, clinical data on rescue strategies in individuals with multidrug-resistant HIV are few. This article describes a patient with extremely drug-resistant HIV-1 with complete resistance to the 4 main ART classes, including second-generation InSTIs. The

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Published April 18, 2024

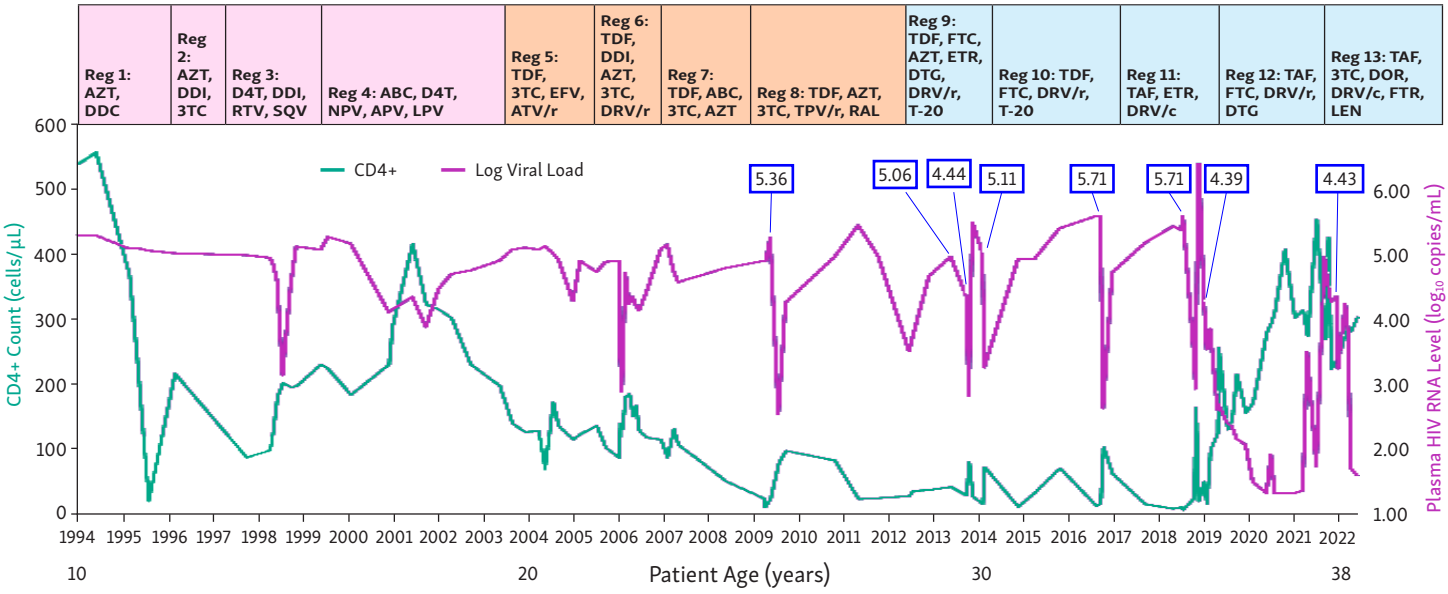

Figure. Evolution of the Antiviral Regimens, Respective CD4+ Counts, and HIV-1 Plasma HIV RNA Levels. x-axis, timeline; y-axis, CD4+ count (cells/µL) in green and plasma HIV RNA level (log_{10} copies/mL) in purple. Values in dark blue boxes represent viral plasma HIV RNA level before hospitalization. The boxes at the top of the graph denote the sequential antiviral regimens, with the color of the boxes related to the degree of HIV resistance; pink boxes indicate HIV resistance to 1 drug within 2 antiviral classes, orange boxes indicate resistance to 3 classes, and light blue boxes indicate resistance to 4 classes.

Abbreviations: /c, boosted with cobicistat; /r, boosted with ritonavir; 3TC, lamivudine; ABC, abacavir; APV, amprenavir; ATV, atazanavir; AZT, zidovudine; D4T, stavudine; DDI, didanosine; DDC, zalcitabine; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; FTC, emtricitabine; FTR, fostemsavir; LEN, lenacapavir; LPV, lopinavir; NPV, nevirapine; Reg, regimen; RAL, raltegravir; RTV, ritonavir; SQV, saquinavir; T-20, enfuvirtide; TAF, tenofovir alafenamide; TDF, tenofovir; TPV, tipranavir.

resistance-associated mutations were investigated by serial genotyping drug resistance tests. Off-label therapies that were implemented for this treatment-experienced patient are described.

Case Report

This patient is a woman who was born in the Democratic Republic of Congo in 1984 and arrived in Belgium in 1993 when 9 years old. Her mother died from AIDS before the patient arrived in Belgium. The patient was diagnosed in February 1993 with HIV-1 and active hepatitis B virus infections. Over the course of the patient's treatment, hepatitis B was inconsistently controlled depending on the compliance with the various treatments covering both HIV and hepatitis B. The Figure summarizes the history of the patient's antiviral regimens and the evolution of her CD4+ T-cell count and plasma HIV RNA level load over time. In 1995, the CD4+ T-cell count was 17/µL and the plasma HIV RNA level was 157,000 copies/mL. The patient was enrolled in a clinical trial and treatment was started with zidovudine 200 mg 3 times daily combined with placebo. After 4 months, she was switched to the active study medication, zalcitabine 0.75 mg 3 times daily and zidovudine (Figure, ART regimen 1). Her first phenotypic drug resistance test, requested because of suboptimal viral suppression, was performed in 1999 with an HIV phenotype antivirogram (Virco NV). The test results triggered an aggressive ART regimen switch to abacavir 300 mg twice daily, stavudine 300 mg twice daily, nevirapine 200 mg twice daily, amprenavir 600 mg twice daily, and lopinavir 200 mg twice daily (Figure, ART regimen 4). However, suboptimal viral control persisted and various attempts were made to achieve viral suppression. Subsequent genotypic drug resistance tests were performed using the Trugene HIV-1 Genotyping Kit (Siemens) or in-house-developed Sanger sequencing techniques on an Applied Biosystems, Inc (ABI) platform (all of which are compliant with International Organization for Standardization 15189 standards) followed by resistance predictions using the Stanford HIV Drug Resistance Database version available at the time of sampling.[14] Resistance-related mutations were investigated in the PR (PI), RT (nRTIs, NNRTIs), INT (InSTIs), and gp120 genes (fostemsavir and maraviroc). Genotypic tropism was predicted using the Geno2Pheno website.[15,16] Therapy changes and dosing were mainly based on the drug susceptibility results available at the time (Table 1). In 2009, the patient was hospitalized with *Pneumocystis jirovecii* pneumonia and diagnosed with

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Table 1. Overview of the Resistance Profiles Available to the Clinicians at Sample Date

Sample date	Oct 11, 1999	Jul 10, 2003	Oct 11, 2004	Jan 23, 2006	Jul 31, 2006	May 10, 2007	Nov 2, 2009	Jun 10, 2011	Nov 17, 2011	Dec 19, 2011	Aug 28, 2012	Dec 20, 2012	Jan 7, 2013	Oct 3, 2013	Aug 31, 2018	Nov 22, 2021	Cumulative
Phenotype (2), virtual phenotype (VP). or genotype (G)	P	G	G	VP	VP	VP	G	G	G	P	G	P	G	P	G	G	G
Treatment at time of resistance profile	D4T, DDI, RTV, SQV	ABC, D4T, NPV, APV, LPV	TDF, 3TC, EFV, ATV/r	TDF, DDI, AZT, 3TC, DRV/r	TDF, DDI, AZT, 3TC, DRV/r	TDF, ABC, 3TC, AZT	TDF, AZT, 3TC, TPV/r, RAL	TDF, AZT, 3TC, TPV/r, RAL	TDF, AZT, 3TC, TPV/r, RAL	TDF, AZT, 3TC, TPV/r, RAL	TDF, FTC, AZT, ETR, DRV/r, DTG, T-20	TDF, FTC, AZT, ETR, DRV/r, DTG, T-20	TDF, FTC, AZT, ETR, DRV/r, DTG, T-20	TDF, FTC, AZT, ETR, DRV/r, DTG, T-20	TAF, ETR, DRV/c	TAF, 3TC, DOR, DRV/c, FTR, LEN	
nRTI																	
Lamivudine (3TC)	ILL	S	S	IR	IR	IR	R	R	R	R	R	R	ILL	R	R	S	R
Abacavir (ABC)	S	R	ILL	R	IR	ILL	R	R	R	R	R	R	R	R	R	R	R
Zidovudine (AZT)	R	R	ILL	ILL	ILL	ILL	R	R	R	R	R	R	R	R	R	R	R
Stavudine (D4T)	S	R	ILL	ILL	ILL	ILL	R	R	R	R	R	R	R	R	R	R	R
Didanosine (DDI)	S	R	R	ILL	ILL	IR	R	R	R	R	R	R	R	R	R	R	R
Emtricitabine (FTC)	–	–	–	R	R	R	R	R	R	R	R	R	ILL	R	R	S	R
Tenofovir (TDF)	–	R	R	IR	IR	ILL	ILL	ILL	ILL	S	R	R	R	R	R	IR	R
NNRTI																	
Doravirine (DOR)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	IR	R
Efavirenz (EFV)	S	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Etravirine (ETR)	-	-	-	-	-	-	R	R	R	S	R	SP	R	SP	R	R	R
Nevirapine (NVP)	S	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Rilpivirine (RPV)	–	–	–	–	–	–	–	–	R	–	R	–	R	–	R	R	R
PI																	
Atazanavir (ATV/r)	–	–	ILL	R	R	IR	R	R	R	R	R	R	R	R	R	R	R
Darunavir (DRV/r)	–	–	–	–	ILL	ILL	IR	IR	IR	SP	IR	SP	IR	SP	R	R	R
Fosamprenavir (FPV/r)	–	–	–	R	R	IR	R	R	R	R	R	R	R	R	R	R	R
Indinavir (IDV/r)	S	R	R	IR	S	ILL	R	R	R	S	R	R	R	S	R	R	R
Lopinavir (LPV/r)	-	R	R	IR	ILL	ILL	R	R	R	SP	R	SP	R	R	R	R	R
Nelfinavir (NFV)	R	R	R	IR	IR	IR	R	R	R	R	R	R	R	R	R	R	R
Ritonavir (/r)	R	R	R	R	–	–	–	–	–	–	–	–	–	–	–	–	–
Saquinavir (SQV/r)	ILL	R	R	IR	ILL	ILL	R	R	R	R	R	R	R	R	R	R	R
Tipranavir (TPV/r)	–	–	–	R	ILL	ILL	ILL	ILL	ILL	SP	IR	SP	IR	SP	R	R	R

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depression and personality disorders. Based on genotypic analysis, treatment was initiated with tenofovir 245 mg daily, lamivudine 150 mg twice daily, zidovudine 300 mg twice daily, tipranavir 500 mg twice daily, ritonavir 200 mg twice daily, and raltegravir 400 mg twice daily (Figure, ART regimen 8), and resulted in a plasma HIV RNA level reduction of 3.3 $\log_{10}$ copies/mL followed by an increase of 1.78 $\log_{10}$ copies/mL 2 months later.

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Table 1. Overview of the Resistance Profiles Available to the Clinicians at Sample Date *(continued from previous page)*

Sample date	Oct 11, 1999	July 10, 2003	Oct 11, 2004	Jan 23, 2006	Jul 31, 2006	May 10, 2007	Nov 2, 2009	Jun 10, 2011	Nov 17, 2011	Dec 19, 2011	Aug 28, 2012	Dec 20, 2012	Jan 7, 2013	Oct 3, 2013	Aug 31, 2018	Nov 22, 2021	Cumulative
InSTI																	
Bictegravir (BIC)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	S	R	R
Cabotegravir (CAB)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	R	R
Dolutegravir (DTG)	–	–	–	–	–	–	–	–	–	S	–	SP	R	R	S	R	R
Elvitegravir (EVG)	–	–	–	–	–	–	ILL	ILL	ILL	–	R	–	R	–	SP	R	R
Raltegravir (RAL)	–	–	–	–	–	–	ILL	ILL	R	R	R	SP	R	R	SP	R	R
Fusion and attachment inhibitors																	
Enfuvirtide (T-20)	–	–	–	–	–	–	–	–	–	S	–	–	–	S	–	–	–
Maraviroc (MVC)	–	–	–	–	–	–	–	CXCR4 use	–	Dual/ mixed CCR5 use predo- mi- nant	–	Dual/ mixed CCR5 use limi- ted	–	Dual/ mixed CCR5 use limi- ted	–	–	–

The cumulative result is based on all mutations detected over time in the genotypic drug resistance tests and interpreted by the current Stanford algorithm, version 9.1. Antiretroviral regimens over time are sequentially expressed and numbered in the upper part of the figure. Antiretroviral medicine names and their abbreviations are presented in column 1. Abbreviations: /c, boosted with cobicistat; /r, boosted with ritonavir; InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ILL, low-level resistance; IR, intermediate resistance; R, high-level resistance; S, susceptible; SP, potential low-level resistance; -, result not available.

The nonpolymorphic mutation in XX (E138K) was already present in 2008. Raltegravir was started in 2009 and the associated polymorphic INT mutation E157Q appeared soon after. According to the Stanford HIV database, the presence of mutations E138K and E157Q should not reduce susceptibility to an InSTI but its scoring system does report low-level resistance to raltegravir and elvitegravir. After 2 years of ART that included raltegravir, mutation Y143R, which is associated with high-level resistance to raltegravir, emerged.

As the therapeutic options were limited, a strategy was designed including intravenous (IV) foscarnet 90 mg/kg/dose twice daily and IV enfuvirtide 90 mg twice daily followed by optimized ART with high-dose dolutegravir and subcutaneous enfuvirtide (Figure, ART regimen 9). Phenotypic susceptibility tests for enfuvirtide were performed in 2011 and 2013, showing conserved drug sensitivity (fold changes, 0.67 and 1.32, respectively). Therapy intensification with IV foscarnet and IV enfuvirtide was repeated in 2014, 2016, and 2018 to attempt viral suppression. However, sustained virologic control was not achieved. Between the periods of regimen intensification with IV antiretrovirals, plasma HIV RNA level increased consistently up to 5.71 $\log_{10}$ copies/mL with CD4+ T cells gradually dropping from 70/µL to 3/µL. In 2019, the patient presented with a wasting syndrome (body mass index, 14 kg/m^2), memory loss, and increasing depression. A progressive multifocal leukoencephalopathy was diagnosed as well as a generalized infection with *Mycobacterium avium* complex, for which adequate treatment was initiated. After multidisciplinary discussion and patient agreement, a gastrostomy was placed because the patient was intolerant to oral antiviral therapy. Thereafter, a new regimen was started with IV foscarnet and enfuvirtide with optimized ART (Figure, ART regimen 12). Acute renal failure and severe myocarditis prompted the discontinuation of foscarnet and the patient was admitted to the intensive care unit until clinical resolution. Three months after the therapy intensification, the patient had gained 12 kg with partial CD4+ T-cell count recovery and had an undetectable plasma HIV RNA level for 18 months. In 2021, the patient developed virologic failure again and a sixth regimen intensification with the same IV molecules was proposed. Mutations S375H/I/M/N/T, M426L/P, M434I/K, and M475I of the envelope glycoprotein 120 HIV-1 gene

related to fostemsavir resistance[16] were not detected in samples from June and November 2021. In January 2021, doravirine 100 mg daily and fostemsavir 600 mg twice daily were added to the regimen. A few months later, the ART regimen was reinforced with oral initiation and thereafter subcutaneous lenacapavir 300 mg administered every 6 months (Figure, ART regimen 13). Viral suppression was achieved in May 2022 with partial immune reconstitution (CD4+ T-cell count, 287/μL), which continued to the date of this report on November 14, 2023 (viral load, <20 copies/mL; CD4+ T-cell count, 364/μL).

Discussion

This case report describes a patient who developed highly drug-resistant HIV with a well-documented evolution of resistance with serial genotyping and phenotyping drug resistance tests.

The patient was perinatally HIV-1 infected and met the definition of AIDS when ART was initiated. When the first drug susceptibility tests were available in 1999, limited resistance-associated mutations were observed. However, after years of suboptimal viral suppression due to severe treatment-adherence issues, a virus almost completely resistant to all drugs in the nRTI, NNRTI, and PI classes was isolated in 2004. From 2004 to 2008, due to the lack of fully active ARV options, the patient was on suboptimal ART. The susceptibility test performed in 2013 demonstrated complete resistance to raltegravir (fold change more than maximal, >100) and dolutegravir (fold change, 21). Several attempts to control HIV replication with innovative strategies were performed, including an induction phase with foscarnet, which is generally used to treat the *Herpesviridae* family of infections. Foscarnet inhibits viral polymerases and has anecdotally been used in regimens for multidrug-resistant HIV.[12,13] Nephrotoxicity is a common adverse effect and cardiotoxicity a rare adverse effect of this drug.[17] It is likely that the reversible myocarditis was linked to foscarnet, because it was acquired in the hospital 1 week after treatment with foscarnet and resolved after the cessation of the drug. Intravenous enfuvirtide was the second drug for the induction phase. Sensitivity to this drug was tested before the treatment, and the IV form was preferred in order to reach higher trough levels, which was suggested in a previous report to treat resistant HIV.[18] In the present report, an induction regimen comprising, among others, IV foscarnet and emfuvirtide, resulted in an effective reduction of the plasma HIV RNA level at each hospitalization (Figure). However, the viral suppression was not maintained, most likely because of adherence problems. On the other hand, no fully effective oral drugs were available after high-level resistance developed in 2018. Fostemsavir was introduced after study results confirmed fostemsavir activity in treatment-experienced individuals.[6] Fostemsavir resistance-associated mutations were detected in drug-experienced individuals with HIV included in a recent trial.[8] The

Table 2. Evolution of the Resistance-Related Mutations Detected in the Genotypic Resistance Profiles

nRTI							
Linked with resistance to	**AZT**	**Accessory**	**3TC/ FTC/ ABC/ TDF**	**AZT**	**ABC**	**ABC/ TDF/ AZT**	**ABC/ TDF/ AZT**
Wild type	**M41**	**E44**	**K65**	**D67**	**L74**	**L210**	**T215**
Oct 11, 2004	41L	44D	65R	67N		210W	215D
Jun 27, 2008	41L	44D		67N	74I	210W	215Y
Nov 2, 2009	41L	44D		67N	74IL	210W	215Y
Jun 10, 2011	41L	44D		67N	74I	210W	215Y
Nov 17, 2011	41L	44D		67N	74I	210W	215Y
Aug 28, 2012	41L	44D		67N	74IL	210W	215Y
Jan 7, 2013	41L	44D		67N		210W	215HPYS
Aug 31, 2018	41L	44D		67N	74I	210W	215Y
Nov 22, 2021	41L	44D		67N	74I	210W	215C

NNRTI							
Linked with resistance to	**RPV/ NVP**	**DOR/EFV/ NVP**	**(ETR/ RPV not well studied)**	**ETR/ NVP/ RPV**	**ETR/ NVP/ RPV**	**EFV/ NVP**	**EFV/ NVP**
Wild type	**K101**	**V106**	**E138**	**V179**	**Y181**	**G190**	**P225**
Oct 11, 2004	101E	106M			181C	190A	
Jun 27, 2008	101E				181C	190A	
Nov 2, 2009	101E	106MV			181C	190A	
Jun 10, 2011	101E				181C	190A	
Nov 17, 2011	101E				181C	190A	
Aug 28, 2012	101E				181C	190A	
Jan 7, 2013	101E				181C	190A	
Aug 31, 2018	101E		138A	179F	181C	190A	225H
Nov 22, 2021	101E				181C	190A	

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Table2. Evolution of the Resistance-Related Mutations Detected in the Genotypic Resistance Profiles *(continued from previous page)*

PI												
Linked with resistance to	**DRV/ FPV/IDV/ LPV/NFV**	**Highly polymorphic but with DRV resistance**	**Minor, all but SQV**	**Minor, all PI**	**Accessory**	**Minor, all but DRV**	**All but TPV**	**Accessory**	**Minor**	**Major, all**	**Accessory but with R to IDV, NFV, FPV, LPV, and DRV**	**All but TPV and DRV**
Wild type	**L10**	**K20**	**V32**	**L33**	**K43**	**M46**	**I54**	**T74**	**V82**	**I84**	**L89**	**L90**
Oct 11, 2004	10F	20R		33F	43T		54V		82A	84V		90M
Jun 27, 2008	10F	20R		33F	43T		54L		82A	84V		90M
Nov 2, 2009	10F	20R		33F	43T		54L		82A	84V		90M
Jun 10, 2011	10F	20R		33F	43T		54L		82A	84V		90M
Nov 17, 2011	10F	20R		33F	43T		54L		82A	84V		90M
Aug 28, 2012	10F	20R		33F	43T		54L		82A	84V		90M
Jan 7, 2013	10F	20R		33F	43T		54L		82A	84V		90M
Aug 31, 2018	10F	20R	32I	33F	43T	46I	54L	74P	82A	84V	89F	90M
Nov 22, 2021	10F	20R	32I	33F	43T	46I	54L	74P	82A	84V	89F	90M

InSTI						
Linked with resistance to	**Accessory**	**RAL/EVG/ DTG**	**Minor EVG**	**EVG**	**All**	**RAL/ EVG/ DTG**
Wild type	**Q95**	**E138**	**Y143**	**S147**	**Q148**	**N155**
Jun 27, 2008		138K				
Nov 2, 2009		138K				
Jun 10, 2011		138KE				
Nov 17, 2011		138K	143R			
Aug 28, 2012	95K	138K		147G	148QR	155H
Jan 7, 2013	95K	138K		147G	148QR	155H
Jul 30, 2013	95K	138K		147G	148R	155H
Aug 31, 2018						
Nov 22, 2021	95K	138K		147G	148R	155H

Abbreviations: 3TC, lamivudine; ABC, abacavir; AZT, xidovudine; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; FPV, fosamprenavir; FTC, emtricitabine; IDV, indinavir; InSTI, integrase strand transfer inhibitor; LPV, lopinavir; NFV, nelfinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitors; NPV, nevirapine; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; SQV, saquinavir; TDF, tenofovir; TPV, tipranavir.

above-mentioned mutations were searched in the samples of the described patient and were not identified. Finally, lenacapavir was added to overcome incomplete viral suppression and seems to have been highly effective in re-pressing this extremely drug-resistant virus, confirming recent studies.[8,19] Susceptibility testing for lenacapavir was not performed, but no pre-existing resistance to lenacapavir has been found in studies, regardless of former treatments.[7,19]

The patient's mental health disorders have hampered the treatment adherence and certainly played a role in incomplete viral suppression. However, the very limited treatment options and, consequently, the burden of ART, have sustained a vicious circle. Gastrostomy, directly observed therapy, and psychiatric follow-up were implemented to improve adherence. The development of easier administration methods than daily oral dosing, as is the case with lenacapavir, may reduce the evolution of resistance in the future.

Conclusion

The well-documented viral genotypic and phenotypic profiles guided clinicians in their treatment strategies over the years and allowed monitoring of the evolution of the HIV-1 strain to 4-class resistance. Highly resistant HIV infection requires a multidisciplinary approach, with practitioners who have extensive expertise in viral infections, mental health problems, and social issues, sometimes leading to unconventional but effective management under close supervision. In heavily experienced individuals with pan-resistant HIV, first-in-class newly available drugs may become an effective strategy to achieve viral suppression.

Acknowledgments

We would like to express our gratitude for the logistic support offered by the medical students of Lila Del Motte, who helped to review the patient's clinical history.

The IAS–USA will identify and resolve ahead of time any possible conflicts of interest that may influence continuing medical education (CME) activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the authors and planners/reviewers are listed below.

Financial relationships with ineligible companies within the past 24 months: Dr Moretti reported no relevant financial relationships with ineligible companies. (Updated April 15, 2024) Dr Stoffels reported no relevant financial relationships with ineligible companies. (Updated April 15, 2024) Dr Van Laethem reported no relevant financial relationships with ineligible companies. (Updated April 15, 2024) Dr Verhofstede reported no relevant financial relationships with ineligible companies. (Updated April 15, 2024) Dr Van Den Wijingaert reported no relevant financial relationships with ineligible companies. (Updated April 15, 2024) Dr Martin reported no relevant financial relationships with ineligible companies. (Updated April 15, 2024)

Reviewer 1 reported consulting or advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and Gilead Sciences, Inc. (Updated January 23, 2024) Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies. (Updated February 7, 2024)

All relevant financial relationships with ineligible companies have been mitigated.

Manuscript received on July 18, 2023, and accepted on December 20, 2023.

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