New Microbiologica, 46, 4, 407-411, 2023, ISSN 1121-7138

CASE REPORT

PRESTIGIO RING: "An 80-year-old man living with HIV resistant to all four antiretroviral classes and desiring treatment simplification"

Maria Mazzitelli[1], Maurizio Zazzi[2], Giulia Marchetti[3], Vincenzo Spagnuolo[4], Maria Mercedes Santoro[5], Emanuele Focà[6], Annamaria Cattelan[1], Antonella Castagna[4]

[1]*Infectious and Tropical Diseases Unit, Padua University Hospital, Padua, Italy;*
[2]*Department of Medical Biotechnology, University of Siena, Siena, Italy;*
[3]*Clinic of Infectious Diseases, San Paolo Hospital, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Italy;*
[4]*Department of Infectious Diseases, IRCSS San Raffaele Scientific Institute, Milan, Italy;*
[5]*Department of Experimental Medicine, University of Rome "Tor Vergata", Rome, Italy;*
[6]*Unit of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili, Brescia, Italy*

SUMMARY

People aging with 4 antiretroviral class resistant HIV are a very challenging population. It is difficult to build up a fully suppressive regimen, and the high prevalence of comorbidities and polypharmacy may cause drug-drug interactions and put adherence at risk. We herein present the case of an 80-year-old man, participating in the PRESTIGIO registry, asking for a reduction in his antiretroviral burden while on polypharmacy for his comorbidities.

Received September 28, 2023 *Accepted* October 16, 2023

CASE PRESENTATION

An 80-year-old heterosexual man harbouring HIV-1 resistant to all the key four antiretroviral classes was recruited in the PRESTIGIO Registry (https://classic.clinicaltrials.gov/ct2/show/NCT04098315) on March 16th, 2022.

He is of Caucasian ethnicity with high education level (medical doctor), has no known allergies, has never smoked, is active regularly, lives with his wife, and is retired. He performed all the vaccinations required according to the current national vaccination schedule. He tested positive for HIV, HIV-1 subtype B strain, in 1990 and a concomitant diagnosis of oesophageal candidiasis was performed. The CD4+ T-cell nadir was 70 cells/mm^3 (8%) and the zenith HIV-1 viral load was 10,500 copies/ml. At the time of referral, his hepatitis B Surface antigen was also positive, and the detection of HBV-DNA was persistently negative.

During 33 years of follow-up, he presented both AIDS and non- AIDS diseases. In 2007, he was diagnosed with a recurrence of oesophageal candidiasis, for which he was treated and cured, and in September 2010 he suffered from a progressive multifocal leukoencephalopathy resolved without clinical sequelae. In 2011, he was diagnosed with and surgically treated for anal cancer, still in complete clinical remission. In 2012, he had disseminated shingles. From 2012 to 2013, he underwent 3 surgical interventions for a recurring abscessed anal fistula.

Regarding antiretroviral treatment, in 1995 he initiated a triple antiretroviral regimen with saquinavir (bought abroad), lamivudine and zidovudine, and since then he has received more than 14 different antiretroviral drugs over his clinical history, belonging to all available antiretroviral classes (see *Table 1*). Despite good adherence to medications, as assessed through pill count and clinic follow-up, he experienced multiple virological failures and the CD4+ T cell counts did not increase significantly, mostly ranging between 100 and 150 cells/mm^3. HIV-RNA suppression was finally achieved and maintained up to the last follow-up visit in January 2017, when he met eligibility criteria for enrolment into the BRIGHTE trial (NCT02362503) (Gartland *et al.*, 2022) as part of the non-randomized cohort and received the novel HIV-1 attachment inhibitor fostemsavir (for which no resistance was detected before starting the drug). In addition to BMS 663068 (2 tablets/day), as opti-

Key words:
Highly treatment experienced, elderly living with HIV, simplification, polypharmacy.

Corresponding author:
Maria Mazzitelli
E-mail: m.mazzitelli88@gmail.com

Table 1 - *Previous antiretroviral therapy, reason of discontinuation and viro-immunological features.*

Dates	*ART*	*Reason for discontinuation*	*HIV RNA copies/ml**	*CD4+ T cell count (cells/mm³)**
1990-1997	No antiretrovirals	–	10,500	70
21/03/1997	SQV+AZT+3TC	Virological failure	Not available	Not available
27/01/1999	NFV+D4T+3TC	Virological failure	Not available	Not available
14/01/2002	3TC/AZT 1 tab x 2/die + LPV/r 2 tabs x 2/die	Virological failure	3,710	150
07/10/2003	TDF +3TC+ LPV 3 tabs x 2/die	Virological failure	19,600	130
07/01/2004	T20+ LPV 3 tabs x 2/die + TDF + 3TC 1 tab x 2/die + ddI 400/die	Virological failure	171,000	120
11/06/2004	AZT+SQR/r + EFV	Virological failure	77,900	130
17/12/2004	3TC/AZT 1 tab x 2/die + NFV + TDF	Virological failure	11,300	120
05/04/2005	FPV/r 2 x 2/die + + T20 2 inj x 2/die + AZT	Virological failure	5,859	50
2006-2008	No information	–	–	–
20/01/2008	DRV/r 1 tab x 2/die + RAL 1 tab x 2/die + ETV 2 tabs x 2/die + TDF/FTC	Virological failure	21,000	110
2008-2011	No information	–	–	–
20/03/2011	DRV/r 1 tab x 2/die + RAL 1 tab x 2/die + ETV 2 tabs x 2/die + TDF/FTC	Virological failure	5,400	90
22/03/2014	MRV 2 tabs/day + DTG 1 tab x 2/die x2 + TDF/FTC	Virological failure	<50 copies/ml for 1 year, then new VF (16/04/2015)	215
22/07/2016	MRV 2 tabs/day +DTG 1 tab x 2/die x2+TDF/FTC+ DRV/r 1 tab x 2/die + SQV 2 tabs x 2/die+T20 inj x 2/die	Virological failure	631,000	150
27/01/2017	FTV 600 x 2/die + TDF/FTC 200/245 mg once daily, MVC 150 mg, 2 tablets twice daily, ETR 100 mg, 2 tablets twice daily, DTG 50 mg twice daily, DRV twice daily, and RTV twice daily + T20 inj (for only 6 months)	Simplification	<50	109
03/01/2018	FTV 600 x 2/die + TDF/FTC 200/245 mg once daily, MVC 150 mg, 2 tablets twice daily, ETR 100 mg, 2 tablets twice daily, DTG 50 mg twice daily	Simplification	<50	189
19/12/2018	TAF/FTC once daily + DTG 50 mg x 2/die + MVC 150 mg, 2 tablets twice daily, ETR 100 mg, 2 tablets twice daily+ FTV 600 x 2/die	–	<50 c	240
10/03/2023	TAF/FTC once daily + DTG 50 mg x 2/die + MVC 150 mg, 2 tablets twice daily + ETR 100 mg, 2 tablets twice daily + FTV 600 x 2/die	–	<50	310
11/09/2023	TAF/FTC once daily + DTG 50 mg x 2/die + ETR 100 mg, 2 tablets twice daily + FTV 600 x 2/die	Simplification	<50	340

3TC = lamivudine; ABC = abacavir; AZT = zidovudine; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; TDF/TAF = tenofovir; TAF = tenofovir/alafenamide; EFV = efavirenz; ETR = etravirine; NVP = nevirapine; RPV = rilpivirine; DOR = doravirine; ATV = atazanavir; DRV = darunavir; FPV = fosamprenavir; LPV = lopinavir; NFV = nelfinavir; SQV = saquinavir; TPV = tipranavir; r = ritonavir; DTG = dolutegravir; RAL = raltegravir; T20 = enfuvirtide; FTV = fostemsavir. *=at the time of start.

mized background therapy (OBT) he received tenofovir diproxil/emtricitabine 200/245 mg once daily, maraviroc 150 mg, 2 tablets twice daily, etravirine 100 mg, 2 tablets twice daily, dolutegravir 50 mg twice daily, darunavir twice daily, and ritonavir twice daily. In addition, subcutaneous injections of enfuvirtide 90 mg twice daily were associated until virological suppression was achieved and maintained. The antiretroviral regimen consisted of 17 tablets a day, to be taken without any food restriction and any fostemsavir dose adjustment. In fact, fostemsavir when co-administered with strong CYP3A inhibitors, P-glycoprotein inhibitors, and modest inducers, including regimens with darunavir/ritonavir, darunavir/cobicistat, and darunavir/ritonavir plus etravirine does not need any dosage modification. After 1 year from achievement of HIV-1 RNA undetectability, darunavir and ritonavir were removed from the regimen, decreasing the pill burden from 17 to 13.

The oral antiretroviral regimen was well tolerated, whereas cutaneous enfuvirtide injections caused significant pain, discomfort, and induration in the site

of injection. To avoid early discontinuation of the drug, we suggested rotating the sites of injection (abdomen, arm, thigh) with a partial clinical response, until virological suppression was achieved.

One year after initiation of maraviroc, the CCR5 tropism performed on DNA was lost, but the regimen achieving HIV RNA undetectability was not modified.

The choice of the antiretroviral regimens was guided by the Genotyping Resistance test (GRT), as strongly recommended by international guidelines (https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf), https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf). The comparison between the cumulative historical genotype and the last one performed on pro-viral DNA is shown in *Table 2*. The historical genotype resulting from multiple Sanger sequencing data obtained from May 2004 to July 2022 showed the following resistance associated mutations: reverse transcriptase M41ML, D67GNW, T69DN, K70R, L74IVW, M184V, T215FV, K219Q, L100I, K103N, Y181C, P225PH; protease V32I, M46I, I54V, V82VA, I84V, L90M; integrase G140S, G148H. In case of antiretroviral regimen simplification, a cumulative genotype offers a more comprehensive evaluation of the burden of resistance compared to the latest available genotype (Garcia *et al.*, 2011), particularly when the latter derives from HIV-1 DNA.

Table 2 - *Comparison of cumulative historical GRT with the last GRT on HIV DNA.*

	Cumulative Historical GRT	*GRT 17/01/2023*
Drug		
NRTI	MRMs: M41ML, D67GNW, T69DN, K70R, L74IVW, M184V, T215FV, K219Q	MRMs: M41L, D67G, T69D, K70R, L74I, M184V, T215FV, K219Q
3TC		
ABC		
AZT		
D4T		
DDI		
FTC		
TAF		
TDF		
NNRTI	MRMs: L100I, K103N, Y181C, P225PH	MRMs: K103N, Y181C, E138Q
DOR		
EFV		
ETR		
NVP		
RPV		
PI	MRMs: V32I, M46I, I54V, V82VA, I84V, L90M	MRMs: V32I, M46I, I54V, V82VA, L90M
ATV/r		
DRV/r		
FPV/r		
IDV/r		
LPV/r		
NFV		
SQV/r		
TPV/r		
INSTI Major Mutations	MRMs: G140S, G148H	MRMs: None
RAL		–
EVG		–
DTG		–
BIC		–
CAB		–

Colours represent the susceptibility of each drug according to the GRT interpretation obtained by the HIVDb algorithm version 9.4 (https://hivdb.stanford.edu): In red, high-level resistance; in orange, intermediate resistance; in yellow, low-level resistance.

NRTI = Nucleoside Reverse Transcriptase Inhibitor; NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor; PI = protease inhibitor; INSTI = integrase strand-transfer inhibitor; 3TC = lamivudine; ABC = abacavir; AZT = zidovudine; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; TDF/TAF = tenofovir; EFV = efavirenz; ETR = etravirine; MRMs = major resistance mutations; NVP = nevirapine; RPV = rilpivirine; DOR = doravirine; ATV = atazanavir; DRV = darunavir; FPV = fosamprenavir; IDV = indinavir; LPV = lopinavir; NFV = nelfinavir; SQV = saquinavir; TPV = tipranavir; r = ritonavir; DTG = dolutegravir; EVG = elvitegravir; RAL = raltegravir; BIC = bictegravir; CAB = cabotegravir. GRT, genotypic resistance testing.

After 12 weeks of treatment in BRIGHTE, despite no remaining active antiretrovirals, the patient achieved virological suppression. Moreover, a significant, even if slow, improvement in the CD4+ T cell count slope was observed.

To date, the man is in good clinical conditions; he regularly performs exercise, reads a lot, is autonomous in daily activities and provides his wife with daily support.

At the last evaluation (September 2023), his vital signs were blood pressure, 150/100 mmHg; pulse rate, 72/min; body temperature, 36.4°C, and respiratory rate, 19/min. His body weight was 68 kg, his height 163 cm, and waist circumference 98 cm. His viro-immunological parameters are stable with undetectable HIV-RNA and 381 CD4+ T cell count (18%), with CD4/CD8 ratio 0.41.

Comorbidities include hypertension, not yet well controlled (he is on a cardiological follow-up now), diabetes managed by diet, osteopenia, prostatic hypertrophy, and dyslipidaemia.

He is on treatment with rosuvastatin 20 mg/daily, silodosin 8 mg/daily, amlodipine 10 mg/daily, Olmesartan/hydrochlorothiazide 20/12.5 mg/daily, cholecalciferol 100,000 UI/ml, monthly. Considering the whole pill burden, the patient is currently taking 17 pills, and he very often asks for simplification of the antiretroviral treatment.

It is worth emphasizing that even if salvage regimens with drugs such as darunavir/ritonavir, etravirine, dolutegravir, either combined with new antiretroviral compounds or not, may guarantee virological success in heavily treatment experienced PLWH, adhering to complex dosing schedules remains challenging in the long run. Side effects, high probability of significant drug-drug interactions, and high pill burden are key issues contributing to loss of adherence. Therefore, ARV simplification is both a challenge and a need in such a difficult-to-treat population, and clinicians must be aware of the possible consequences of complex ARV regimens at the individual and community level. In fact, long term exposure to multiple tablet regimens and failure to timely switch may eventually result in loss of adherence, viral rebound, and potential transmission of a multidrug resistant virus.

Choice of the new antiretroviral regimen and follow-up

The PRESTIGIO group discussed the possible following strategies:

1) Maintaining the currently successful regimen, since viral load undetectability remains the most important goal in people with resistance to all 4 antiretroviral drugs and considering that his immunological parameters are slowly but consistently improving (CD4+ T cell count increased from 150, before starting fostemsavir in 2016, to 381 cell/mm^3 in 2023).
2) Removing from the regimen etravirine and maraviroc and adding to the combination doravirine (according to the last genotype which was performed on DNA), maintaining TAF/FTC, dolutegravir twice daily and fostemsavir twice daily, by strictly monitoring viral load.
3) Removing from the regimen etravirine and maraviroc, while maintaining TAF/FTC, dolutegravir twice daily and fostemsavir twice daily, and strictly monitoring viral load. CCR5 tropism was lost soon after 1 year from maraviroc initiation and the virus became X4. By removing etravirine, plasmatic concentrations of dolutegravir are expected to increase, further warranting virological suppression. In case of failure, adding subcutaneous injectable lenacapavir every 6 months may be considered.

The introduction of doravirine was widely discussed for its favourable resistance profile against viruses harbouring NRTI and NNRTI resistance associated mutations (Saladini F *et al.*, 2023; Brenner *et al.*, 2023), but finally not adopted to keep a rescue drug in case of virological failure.

Therefore, the PRESTIGIO group, after a multidisciplinary discussion including clinicians and virologists, decided the following strategy. The first step is to remove maraviroc from the regimen and to control viral load every two weeks. The second step foresees the removal of etravirine (which is a drug with high-level resistance at the historical genotype), followed by viral load monitoring every two weeks, and maintenance of a regimen made of dolutegravir 50 mg x 2/die (because of intermediate resistance to the last genotype) + fostemsavir 600 mg x 2/die + tenofovir/alafenamide/emtricitabine 200/25 mg once daily (for its residual activity due to intermediate resistance of TAF and a possible benefit in terms of viral fitness and to treat HBV). A strict follow-up will be implemented to monitor virological control. This simplification strategy removes a considerable number of tablets from the regimen. A further discussion was conducted regarding the possible use of intramuscular injections of lenacapavir as a rescue drug to be added in case of loss of virological control.

On July 5th, 2023, maraviroc was removed from the regimen, and on September 9th, 2023, HIV RNA, which was monitored biweekly from July, is still <50 copies/ml. A close monitoring of HIV-RNA is still ongoing.

Considering the long-life expectancy for people living with HIV under successful antiretroviral therapy, clinicians are expected to manage a limited but challenging proportion of people living with a multidrug resistant virus with concurrent multimorbidity and polypharmacy, and specialised clinics and services have been implemented for this purpose. In this scenario, introduction of novel antiretroviral agents and

simplification strategies to reduce pill burden and improve both adherence and quality of life must be wisely integrated to maintain long-term viro-immunological control. However, further studies are needed from real settings of people aging with 4 antiretroviral class resistant HIV.

Consent for publication

Written informed consent was obtained for the publication of this case report. The person herein described was enrolled in the PRESTIGIO registry, and his case was discussed during the PRESTIGIO RING, a quarterly Italian virtual meeting where clinicians, virologists, pharmacologists, and other experts regularly discuss complex clinical cases of PLWH with multi-drug resistance, with the goal of optimizing treatment (Labate *et al*., 2023). The PRESTIGIO Registry is an Italian, observational, prospective, multicentre annual collection of data on clinical, laboratory, treatment, and virological characteristics of PLWH with four-drug class resistance, approved in 2017 (NCT04098315). PRESTIGIO Registry activities are supported by ViiV Healthcare, Gilead Sciences, Merck Sharp & Dohme (MSD).

Acknowledgments

We thank all centres participating in the PRESTIGIO registry for their high quality and continuous work.

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