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CASE REPORT

PRESTIGIO RING "a 59-year-old man with multidrug resistant HIV-1 infection failing a regimen including dolutegravir, rilpivirine, atazanavir/cobicistat: successful treatment tailoring based on genotypic and phenotypic resistance tests"

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PRESTIGIO is an Italian, observational, prospective, multicentre cohort collecting data on clinical, laboratory, treatment, and virological characteristics of people living with HIV with four-drug class resistance, approved in 2017 (NCT04098315)

SUMMARY

Management of virological failure in heavily treatment-experienced people with multidrug-resistant (MDR) HIV infection is a serious clinical challenge. New drugs with novel mechanisms of action have recently been approved, and their use has improved the outcome of subjects with limited treatment options (LTO). In this setting, the choice of antiretroviral therapy (ART) should be tailored based on the pattern of resistance, treatment history and patients' individual characteristics. While genotypic resistance testing is the reference method for analysing residual drug susceptibility, phenotypic resistance testing can provide additional support when facing LTO. Herein, we present the case of a patient with MDR HIV-1 infection on virological failure enrolled in the PRESTIGIO Registry. The salvage ART regimen, which included drugs with novel mechanisms of action (MoA), was tailored to the patient's clinical characteristics and on the resistance pattern explored with genotypic and phenotypic investigation, allowing the achievement of viro-immunological success. The use of recently approved drugs with novel MoA, combined with an optimized background regimen, may also achieve virological suppression in people with LTO.

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CASE PRESENTATION

A 59-year-old heavily treatment-experienced (HTE) man, infected with subtype B human immunodeficiency virus-1 (HIV-1) resistant to all four main antiretroviral classes [nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (InSTIs)], came to the outpatient clinic of the Infectious and Tropical Diseases Unit of the University of Siena in June 2010.

The patient was a Caucasian man, with a history of multiple high-risk heterosexual relations. He tested positive for HIV-1 on 2001, when he was diagnosed with acquired immune deficiency syndrome (AIDS) due to a *Pneumocystis jirovecii* pneumonia, cytomegalovirus infection and oesophageal candidiasis. From 2001 to 2010 the patient was treated at another clinic and, at the time of our first evaluation, neither viral load before antiretroviral therapy (ART) initiation nor CD4+ T cell count was available. Likewise, previous antiretroviral treatment lines were not documented in detail, but an exposure to NRTIs, NNRTIs, boosted/unboosted PIs and InSTIs was reported. Moreover, the patient reported multiple virological

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failures, poor adherence, and poor gastrointestinal tolerability to ART, resulting in the prescription of suboptimal antiretroviral regimens in the past. The patient was in good clinical condition, with only minor comorbidities (anal HPV-73 infection and asymptomatic biliary lithiasis).

At the time of our first visit, the patient was on therapy with tenofovir disoproxil fumarate 245 mg once daily plus etravirine 200 mg twice daily plus raltegravir 400 mg twice daily. Plasma HIV-RNA was 20,130 copies/mL and CD4+ T cells count was <200/mm^3. A genotyping resistance test (GRT) on plasma HIV-RNA performed at admission by Sanger sequencing showed the following resistance associated mutations (RAMs): D67N, T69D, K70R, T215F and K219Q for NRTIs, A98G for NNRTIs and several major muta-

Table 1 - *Genotyping Resistance test (GRT) on HIV-RNA performed by Sanger sequencing on June 2010 and historical GRT performed on August 2021.*

Drugs	*GRT on RNA June 2010*	*Historical GRT August 2021*
NRTI	*RAMs:* 67N, 69D, 70R, 215F, 219Q	*RAMs:* 41L, 67N, 69D, 70R, 184V, 215CF, 219Q, 238T
3TC/FTC		
ABC		
AZT		
D4T		
DDI		
TDF/TAF		
NNRTI	*RAMs:* 98G	*RAMs:* 98G, 101P, 181CI
DOR		
EFV		
ETR		
NVP		
RPV		
PI	*RAMs:* 46I, 48V, 54T, 82A, 90M	*RAMs:* 32I, 33F, 46IV, 48V, 50V, 54T, 82A, 90M
ATV/r		
DRV/r		
FPV/r		
IDV/r		
LPV/r		
NFV		
SQV/r		
TPV/r		
INSTI	*RAMs:* not performed	*RAMs:* 97A, 138T, 140S, 148H
RAL		
EVG		
DTG		
BIC		
CAB		
MVC	Not performed	
T20	Not performed	

Colors represent the susceptibility of each drug according to the GRT interpretation obtained by the HIVDb algorithm version 9.5.1 (https://hivdb.stanford. edu): In red, high-level resistance; in orange, intermediate resistance; in yellow, low-level resistance; in dark green, potential low-level resistance; in bright green, no resistance.

NRTI = Nucleoside Reverse Transcriptase Inhibitor; NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor; PI = protease inhibitor; INSTI = integrase strand-transfer inhibitor; 3TC = lamivudine; FTC = emtricitabine; ABC = abacavir; AZT = zidovudine; D4T = stavudine; DDI = didanosine; TDF/TAF = tenofovir disoproxil/ fumarate; DOR = doravirine; EFV = efavirenz; ETR = etravirine; NVP = nevirapine; RPV = rilpivirine; ATV = atazanavir; DRV = darunavir; FPV = fosamprenavir; IDV = indinavir; LPV = lopinavir; NFV = nelfinavir; SQV = saquinavir; TPV = tipranavir; r = ritonavir; RAL = raltegravir; EVG = elvitegravir; DTG = dolutegravir; BIC = bictegravir; CAB = cabotegravir; MVC = maraviroc; T20 = enfuvirtide; GRT, genotypic resistance testing. RAMS= resistance associated mutations.

tions (M46I, G48V, I54T, V82A, L90M) for PIs, conferring resistance to all available PIs except for darunavir, according to Stanford HIVdb interpretation rules (https://hivdb.stanford.edu, version 9.5.1) (*Table 1*). M184V was not detected at that time, but was identified in previous GRTs performed in a different laboratory, while the relative sequences were retrieved from the ARCA database (https://www.dbarca.net). Sequencing of the integrase coding region was not performed at this time.

Based on this genotypic resistance pattern, ART was switched to darunavir/ritonavir 600/100mg twice daily plus etravirine 200 mg twice daily plus tenofovir disoproxil fumarate 245 mg once daily. However, due to poor gastrointestinal tolerability to darunavir/ritonavir, the patient self-discontinued this regimen.

Subsequently, from 2010 to 2016, he was exposed to more than 12 lines of treatment, all modified for virological failure, gastrointestinal intolerance (mainly related to PIs), and poor adherence. The patient was thus exposed to all four main antiretroviral classes over the years, particularly to: the NRTIs tenofovir disoproxil fumarate or alafenamide, lamivudine, and emtricitabine; the NNRTIs etravirine and rilpivirine; the PI darunavir and the InSTIs raltegravir and dolutegravir, both once and twice daily. He was also exposed to the entry inhibitors maraviroc and enfuvirtide. Over these years, plasma HIV-RNA always remained detectable, with average values over 3 $\log_{10}$ copies/mL. CD4+ T cell count gradually decreased from 350 cells/mm^3 in 2014 to 200 cells/mm^3 in 2016, then stably remaining below this value up to 2021. Since 2010, multiple GRTs on HIV-RNA were performed by Sanger sequencing, showing the appearance of new RAMs (see *Table 1* for historical GRT). Exposure to lamivudine or emtricitabine led to the re-emergence of M184V, while the use of raltegravir and dolutegravir selected mutations eventually causing cross-resistance for InSTIs. After 2019, additional RAMs for PIs (V32I, L33F and I50V) and NNRTIs (K101P and Y181I) caused the reduction of susceptibility to darunavir (now predicted to be associated with intermediate resistance) and high-level resistance for all the NNRTIs except for doravirine, predicted with intermediate resistance.

A genotypic coreceptor test predicted R5 tropism and thus susceptibility to maraviroc according to Geno2Pheno algorithm. The false positive rate (i.e., the probability that a V3-sequence is falsely predicted as CXCR4 tropic) was 26%, above the cut-off of 10% used to predict CXCR4 tropism when using Sanger sequencing as recommended by the European Consensus Group on clinical management of HIV-1 tropism testing (Vandekerckhove *et al.*, 2011). No RAMs for enfuvirtide were detected within the gp41 coding region.

Based on the results of the cumulative GRT, the patient was defined as infected by multidrug resistant (MDR) HIV-1 and was enrolled in the PRESTIGIO Registry on 22nd October 2018 (Clemente *et al.*, 2024). In October 2021, the patient was on therapy with atazanavir/cobicistat 300/150 mg once daily plus dolutegravir/rilpivirine 50/25 mg once daily, had HIV-RNA of 69,500 copies/mL and showed a progressive decrease of absolute CD4+ cells count [from 131 cells/mm^3 (with CD4% 13.2% and CD8 647 cells/mm^3) to 115 cells/mm^3 (with CD4% 12.4% and CD8 618 cells/mm^3) and then 82 cells/mm^3 (with CD4% 12.6% and CD8 463 cells/mm^3)].

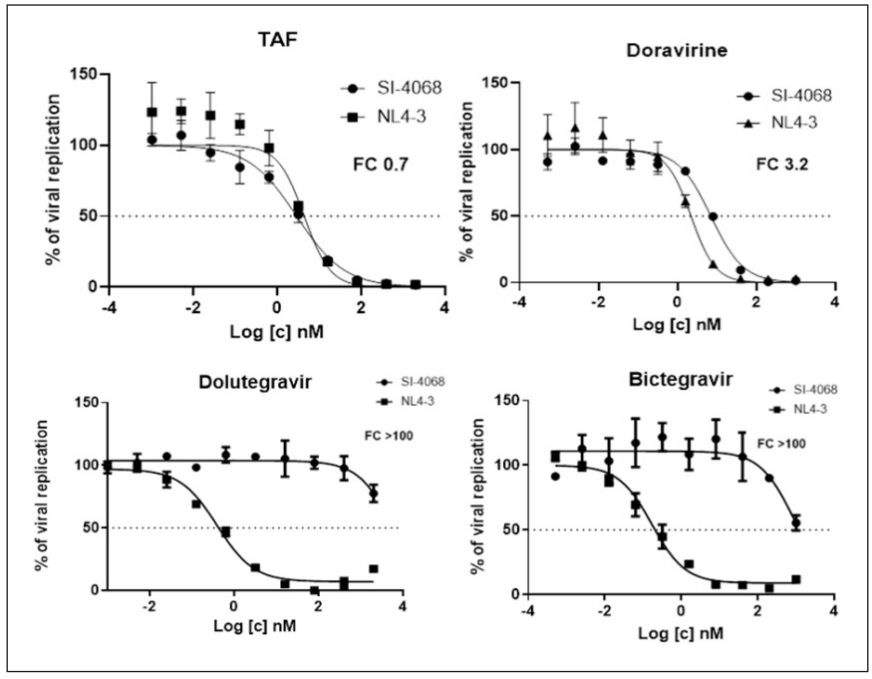

Figure 1 - *Phenotypic resistance test for tenofovir alafenamide (TAF), doravirine, dolutegravir and bictegravir; FC = fold change; NL4-3, reference wild type virus; SI-4068, patient's virus.*

Despite the alarming viro-immunological status, the patient was in good clinical condition under secondary prophylaxis with cotrimoxazole and did not develop significant clinical events nor opportunistic infections.

Due to the limited treatment options remaining, an in-depth virological assessment was performed to better define the resistance pattern. Phenotypic resistance testing (PRT) was performed to measure the in vitro activity of reverse transcriptase and integrase inhibitors (see *Figure 1*), expressed as fold-change (FC) with respect to the inhibitory activity against the wild-type reference NL4-3 strain (Saladini et al., 2018). Where available, Monogram Phenosense clinical or biological FC cut-offs were used to predict in vivo activity from in vitro FC values. Tenofovir had a FC value of 0.7, indicating full susceptibility, while the FC value of 3.2 calculated for doravirine was slightly higher than the biological cut-off (FC=3), indicating minimally reduced susceptibility (Asante-Appiah et al., 2021). High-level resistance to the InSTIs bictegravir and dolutegravir was confirmed by PRT, with both drugs showing FC values >100.

In addition, gp120 sequencing revealed the lack of known mutations associated with resistance to fostemsavir, while the presence of two potential glycosylation sites within the V5 domain suggested full susceptibility to ibalizumab.

Considerations on Phenotypic resistance testing and new drug classes resistance testing

PRT is not routinely performed in clinical practice, as it is technically challenging, not available in all laboratories, expensive, and time-consuming. However, it could be useful in selected patients in whom complex patterns of drug-resistance are observed with the GRT and for whom, therefore, limited treatment options are available.

In this clinical case, the use of PRT allowed us to better understand the extent of resistance to InSTIs, demonstrating their likely ineffectiveness even at higher off-label doses (e.g., dolutegravir 100 mg twice daily) (Ferrari *et al.*, 2019; Fulco *et al.*, 2020). On the other hand, doravirine retained activity and could therefore be included in the rescue regimen, given that the PRT showed a fold change close to the drug's susceptibility cut-off.

The use of susceptibility testing for drugs belonging to newer classes is not recommended in routine clinical practice (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents.), since the clinical impact of HIV-1 natural variability is still unclear (e.g., fostemsavir and ibalizumab) or close to zero due to the absence of RAMs in circulating strains (e.g., lenacapavir) (Toma *et al.*, 2011; Marcelin *et al.*, 2020; Gartland *et al.*, 2021; Nka *et al.*, 2022). However, the use of fostemsavir in PLWH harbouring CRF01_AE is not recommended due to natural resistance (Zhou *et al.*, 2014).

By contrast, resistance testing for new drug classes might be an added value at treatment failure to investigate genotypic and/or phenotypic changes from baseline, thus helping to support clinical decisions for the re-use of drugs in subsequent salvage therapies.

Choice of the new antiretroviral regimen and follow-up:

The PRESTIGIO group discussed the possible following strategies to establish a rescue regimen for this patient:

1. Design a regimen based only on drugs of old classes with high genetic barrier, showing residual antiviral activity (e.g., darunavir and dolutegravir), given at higher dosages.
2. Define an optimized background regimen (OBR) with high genetic barrier drugs of old classes (e.g., darunavir and dolutegravir) with the addition of drugs from new classes.
3. Define an OBR tailored to patient's characteristics plus the addition of drugs from new classes.

High genetic barrier drugs as darunavir and dolutegravir are commonly used in people with MDR HIV-1 infection, as these molecules are the ones that usually retain residual activity, especially when given at high dosages. However, their activity in clinical practice could be limited by various mechanisms of viral resistance or by patients' tolerability.

In our case, the patient referred previous intolerance to all PIs, which led to poor treatment adherence over time; therefore, the panel decided not to include darunavir in the OBR. For dolutegravir, very high resistance in both GRT and PRT was observed, and therefore this drug was not considered an option in the rescue regimen.

Drugs with novel mechanisms of action (MoA) have shown good efficacy when used with an OBR in the setting of MDR HIV-1 infection (Emu *et al.*, 2018; Kozal *et al.*, 2020; Segal-Maurer *et al.*, 2022). However, at the time we visited the patient, access to these drugs was limited, as some were available only in the setting of clinical trials or for compassionate use (e.g., lenacapavir, islatravir).

After a multi-disciplinary discussion including clinicians and virologists, the PRESTIGIO group favoured a tailored OBR based on drugs from old classes with residual antiviral activity and with proven adequate tolerability, plus the addition of drugs with a novel MoA.

Based on these considerations, a salvage regimen consisting of emtricitabine/tenofovir alafenamide + doravirine + maraviroc + fostemsavir was selected. The addition of ibalizumab was proposed but refused by the patient, who could not come to the hospital every 14 days to receive the drug infusion.

The salvage regimen was chosen with two main objectives:

1) improve the patient's adherence to ART by selecting highly tolerated drugs, and

2) increase the number of active molecules by adding drugs with novel MoA, to which the patient had never been exposed.

Moreover, a symmetric regimen was designed to improve the patient's adherence (Murri *et al.*, 2010). On the basis of the historical genotype, the genotypic susceptibility score (GSS) (DeLuca *et al.*, 2003) of the salvage regimen was 3 (0 point for emtricitabine; 0.5 point for tenofovir alafenamide and doravirine; 1 point for maraviroc and fostemsavir).

Viro-immunological response after initiation of tailored ART

The selected salvage regimen was started in November 2021. Fostemsavir was not immediately available at our centre; therefore, considering the rapid decline of CD4+ cell count and the possible occurrence of opportunistic infections, an initial regimen with emtricitabine/tenofovir alafenamide 200/25 mg once daily + doravirine 100 mg once daily + maraviroc 300 mg twice daily (OBR) was immediately started. Fostemsavir 600 mg twice daily was then added after three months, when it became available. In the first 3 months after new ART initiation, plasma HIV-RNA rapidly declined from more than 5 log copies/mL to 2 log copies/mL, and absolute CD4+ cells count increased from 84 cells/mmc to more than 200 cells/mmc (with CD4% 11.5% and CD8 1425 cells/mm^3). Following the addition of fostemsavir, plasma HIV-RNA decreased further and CD4 cells count progressively increased, reaching stable levels above 300 cells/mm^3. Up to the subsequent follow-up, the patient reported high adherence to the new tailored ART and good tolerability, without any adverse event. At the last visit (28 months after starting the salvage regimen), the patient was in good clinical condition, and no opportunistic infections or non-AIDS-related events occurred. Last plasma HIV-RNA was 45 copies/mL and absolute CD4+ T cells count was 356/mm^3 (with CD4% 20.2% and CD8 1051 cells/mm^3) (see *Figure 2* for detailed viro-immunological response over time).

Discussion and Conclusions

Current guidelines state that, when facing virological failure, at least two fully active antiretroviral drugs (one of which with high resistance barrier) should be included in salvage regimens (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents; EACS European AIDS Clinical Society).

However, patients with MDR HIV-1 infection often have limited treatment options, as the activity of drugs with high genetic barrier may be compromised by extensive resistance. Moreover, some valuable treatment options may have to be ruled out due to poor individual tolerability.

Therefore, the interplay between virological and clinical aspects makes the choice of salvage regimens for MDR HIV-1 a complex task, in which each regimen needs to be tailored to the patient's individual characteristics.

In our case, a successful viro-immunological response was obtained even if drugs with high genetic barrier were not included in the rescue regimen. This success was achieved through an in-depth virologic characterization, which included

1) the evaluation of historical GRT, which detailed the acquisition of resistance over time;
2) the use of PRT, which allowed us to better define the degree of resistance to the available drugs at the time of failure, and
3) the use of GRT for drugs with novel MoA, which allowed us to exclude pre-treatment resistance patterns that could limit the efficacy of some drugs (e.g., fostemsavir).

Moreover, virological aspects were integrated with

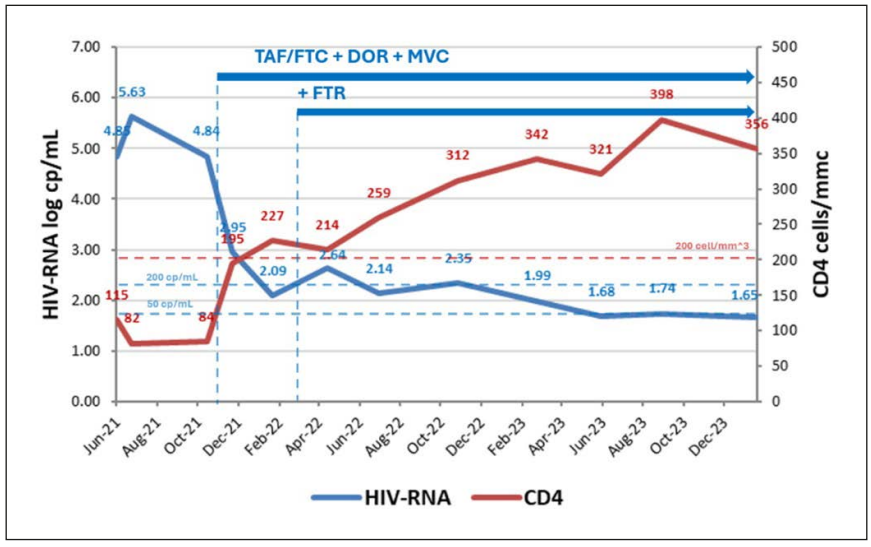

Figure 2 - *Evolution of viro-immunological parameters after the introduction of the salvage regimen.*

the patient's clinical history (e.g., intolerance to PI) leading us to exclude from the salvage regimen some drugs with high genetic barrier and partially retained activity (e.g., darunavir), but not previously tolerated by the patient. This comprehensive clinical and virological evaluation was the basis of viro-immunological success in our patient.

A sharp increase in CD4 cells count was observed in the first three months after the OBR was initiated (from 84 to 214 cells/mm^3). Thereafter, CD4 cells count continued to increase when fostemsavir was added, allowing a CD4 recovery of nearly 260 cells/mm^3 over two years. This is in agreement with the results of the BRIGHTE trial, showing a relevant increase in CD4+ cells count over time, which was sustained for 240 weeks (Aberg *et al*., 2023). Although no direct comparisons with other drugs are available, current studies seem to suggest an interesting immunological evolution in patients treated with fostemsavir. Several hypotheses have been proposed to explain the potential immunological benefits of fostemsavir. Temsavir may prevent interactions between soluble gp120 and CD4+ cells, thus limiting their activation, preventing antibody-dependent cellular cytotoxicity, cytokine burst and induction of apoptosis (Richard *et al*., 2023). However, these hypotheses are not yet confirmed, and further studies are needed to understand the potential immunological benefits of fostemsavir. Moreover, it should also be emphasized that immunological success is usually dependent on the choice of the OBR, which should be tailored based on genotypic and phenotypic resistance tests to allow maximal virological suppression.

In conclusion, in HTE people with MDR HIV-1 on virological failure, every effort should be made to thoroughly characterize the resistance pattern, and the use of both GRT and PRT could be considered in selected situations to guide the choice of salvage regimens. When addressing the clinical dilemma of which drugs to include in salvage regimens, clinicians need to consider not only virological aspects (e.g., resistance, genetic barrier) but also clinical/therapeutic history and patients' individual characteristics, since tolerability and convenience of regimens are critical aspects for the achievement of adequate adherence, which is in turn essential for clinical success. In recent years, new drugs with novel MoA and good tolerability have become available (e.g., fostemsavir, ibalizumab, lenacapavir), and their inclusion in salvage regimens has also achieved high rates of virological success in people with limited treatment options.

Consent for publication

Written informed consent was obtained for data collection and publication. 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; Mazzitelli *et al*., 2024). 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; https://registro-prestigio.org/).

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