# How to choose the optimized background therapy with fostemsavir in viremic people with multidrug-resistant HIV?
## A clinical case

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## BACKGROUND

New antiretrovirals, such as FTR, offer a unique opportunity for people with multidrug-resistant HIV to achieve and maintain viral suppression, especially if a regimen with ≥2 active molecules can be designed.[1,2]
We report a case in which, although there were apparently no treatment options according to genotypic resistance testing, phenotypic resistance testing helped to select an optimized background therapy for combination with FTR.

## CLINICAL CASE

May 2016: a 53-year-old man living with 4-class drug-resistant HIV had uncontrolled viral replication (HIV-1 RNA: 1668 copies/mL, CD4⁺ 641 cells/μL, CD4⁺/CD8⁺ ratio 0.43) despite a complex antiretroviral regimen containing DTG 50 mg bid + ETR 200 mg bid + DRV/r 600/100 mg bid + F/TDF 200/245 mg qd (Figure 1).

- HIV infection since January 1995, antiretroviral therapy (ART) since May 1996, resistance to ≥1 NRTI, ≥1 NNRTI, ≥1 PI and ≥1 INSTI since March 2010.
- CDC stage B2, CD4⁺ nadir 305 cells/μL.
- Previous exposure to AZT, 3TC, FTC, ddC, d4T, ddI, TDF, EFV, ETR, SQV, IDV (±r), NFV, fAPV/r, ATV/r, DRV/r, RAL, and DTG.
- Comorbidities: arterial hypertension, lipoatrophy, dyslipidemia (May 2016: total cholesterol 202 mg/dL, HDL 47 mg/dL, LDL 103 mg/dL, triglycerides 280 mg/dL), carotid stenosis, impaired fasting glucose, previous non-ST elevation myocardial infarction (2011), previous HCV (positive anti-HCV antibodies) and HBV (positive anti-HBs and anti-HBc, negative HBs antigen) infections.
- Comedications: rosuvastatin 20 mg qd, metoprolol 25 mg bid, acetylsalicylic acid 100 mg qd.
- Cumulative data from all the available genotypic resistance tests (December 2015): no fully active antiretroviral drugs (Table 1).
- Tropism (April 2016): CXCR4.
- Combined genotypic + phenotypic resistance test (April 2016): phenotypic susceptibility to ATV/r, IDV/r, and TPV/r (Table 1).
- Antiretroviral therapy switched to FTR 600 mg bid + DTG 100 mg bid + ATV/r 300/100 mg qd + F/TDF 200/245 mg qd (May 2016).

Since June 2016: virological suppression (HIV-1 RNA <50 copies/mL).

- Dose reduction of DTG to 50 mg bid after detection of a through plasmatic concentration of 15843ng/mL with no evidence of toxicity (July 2020)
- Switch from F/TDF to F/TAF 200/10 mg qd (June 2017) to prevent potential toxicity.
- Switch from ATV/r to ATV/c 300/150 mg qd in order to reduce pill burden.
- Unexpected immulogic recovery with a CD4⁺ peak of 1920 cells/μL (December 2017) and a CD4⁺/CD8⁺ peak of 0.76 (at the last visit).
- Diagnosis of type II diabetes (2021).

September 2023 (last visit): HIV-1 RNA <50 copies/mL, CD4⁺ 1385 cells/μL, CD4⁺/CD8⁺ 0.76.

## CONCLUSIONS

New tools to complement genotypic resistance testing in people with multidrug-resistant HIV are needed, in order to select the optimized background therapy for combination with a novel antiretroviral.
Although phenotypic resistance testing may be difficult to access, it could be a valuable resource when effective treatment options appear to be lacking.

**Figure 1. HIV-1 RNA, CD4⁺ T-cell count, and antiretroviral therapy from January 2011 to September 2023**

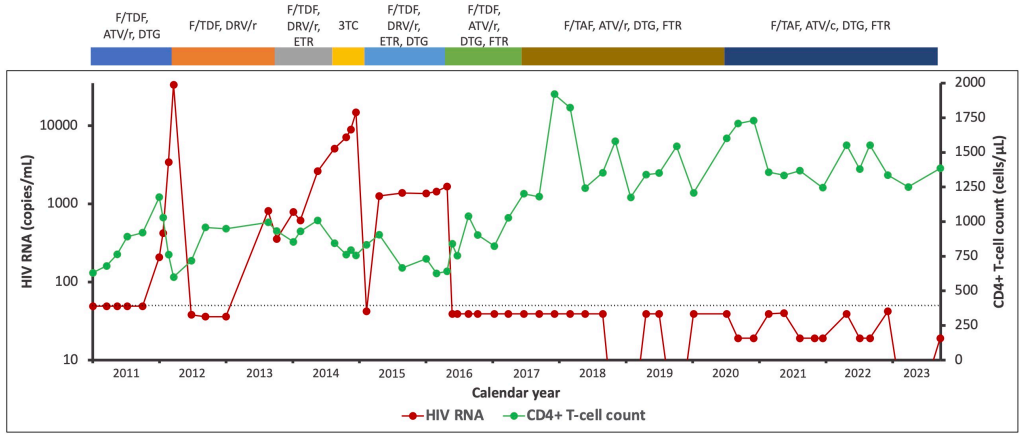


**Table 1. Available data on resistance until May 2016**

| | Last genotypic resistance test (December 2015) | Cumulative data from genotypic resistance tests (December 2015) | Combined genotypic + phenotypic (April 2016) | |
|---|---|---|---|---|
| | | | Phenotype | Genotype |
| **NRTI + NNRTI resistance-associated mutations** | **NRTI:** M41L, A62V, D67N, V75I, M184V, L210W, T215Y, K219R - **NNRTI:** K103N, E138G, Y188L, K238T - **Other:** I31L, T39A, K43Q, V90I, K122E, S162Y, R172K, V179I, G196E, T200A, E203D, R211K, D237N | **NRTI:** M41L, A62V, D67N, V75I, M184IV, L210W, T215EY, K219ER - **NNRTI:** K103N, E138G, Y188L, H221Y, K238T - **Other:** I31L, T39A, K43Q, V90I, K122E, S162Y, R172K, V179I, G196E, T200A, E203D, R211K, D237N | **NRTI:** M41L, A62V, D67N, V75I, M184V, L210W, T215Y, K219R - **NNRTI:** V90I, K103N, E138G, V179I, Y188L, K238T | |
| **Abacavir (ABC)** | High-level resistant | High-level resistant | Partially sensitive | Resistant |
| **Didanosine (ddI)** | High-level resistant | High-level resistant | Partially sensitive | Resistant |
| **Emtricitabine (FTC)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Lamivudine (3TC)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Stavudine (d4T)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Zidovudine (AZT)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Tenofovir (TDF)** | High-level resistant | High-level resistant | Partially sensitive | Resistant |
| **Delavirdine (DLV)** | - | - | Resistant | Resistant |
| **Efavirenz (EFV)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Etravirine (ETR)** | Low-level resistant | Intermediate resistant | Resistant | Resistant |
| **Nevirapine (NVP)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Rilpivirine (RPV)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Doravirine (DOR)** | High-level resistant | High-level resistant | - | - |
| **PI resistance-associated mutations** | **Primary:** V32I, M46I, I47V, I50V, I54L, L90M - **Accessory:** L33F - **Other:** L10I, I13V, G16E, L19I, K20R, E35D, M36I, P39S, L63P, I66F, A71V, V82I, I85V, Q92R | **Primary:** V32I, M46I, I47V, I50V, I54L, L90M - **Accessory:** L33F - **Other:** L10I, I13V, G16E, L19I, K20R, E35D, M36I, P39S, K55R, L63P, I66F, K70E, A71V, V82I, I85V, Q92R | L10I, V11I, I13V, K20R, V32I, L33F, E35D, M36I, M46I, I47V, I50V, I54L, A71V, V82I, I85V, L90M | |
| **Atazanavir (ATV)** | - | - | Resistant | Resistant |
| **Atazanavir/ritonavir (ATV/r)** | High-level resistant | High-level resistant | Sensitive | Resistant |
| **Darunavir/ritonavir (DRV/r)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Fosamprenavir/ritonavir (FPV/r)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **indinavir/ritonavir (IDV/r)** | High-level resistant | High-level resistant | Sensitive | Resistant |
| **Lopinavir/ritonavir (LPV/r)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Nelfinavir (NFV)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Ritonavir (RTV)** | - | - | Resistant | Resistant |
| **Saquinavir/ritonavir (SQV/r)** | High-level resistant | High-level resistant | Partially sensitive | Resistant |
| **Tipranavir/ritonavir (TPV/r)** | Intermediate resistant | Intermediate resistant | Sensitive | Sensitive |
| **INSTI resistance-associated mutations** | **Primary:** G140S, Q148H - **Accessory:** none - **Other:** D3E, E10D, M154I, V165I, V201I, I208L | **Primary:** G140S, Q148H - **Accessory:** none - **Other:** D3E, E10D, M154I, V165I, V201I, I208L | T97A, E128K, G140S, Q148H | |
| **Dolutegravir (DTG)** | Intermediate resistant | Intermediate resistant | Resistant | Resistant |
| **Elvitegravir (EVG)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Raltegravir (RAL)** | High-level resistant | High-level resistant | Resistant | Resistant |
| **Bictegravir (BIC)** | Intermediate resistant | Intermediate resistant | - | - |
| **Cabotegravir (CAB)** | High-level resistant | High-level resistant | - | - |

### References

1. Kozal M, Aberg J, Pialoux G, et al. **Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection**. *N Engl J Med* 2020. doi: 10.1056/NEJMoa1902493.
2. Aberg JA, Shepherd B, Wang M, et al. **Week 240 Efficacy and Safety of Fostemsavir Plus Optimized Background Therapy in Heavily Treatment-Experienced Adults with HIV-1**. *Infect Dis Ther* 2023. doi: 10.1007/s40121-023-00870-6.

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