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NOVEL ID CASES

Sustained HIV Viral Suppression With Dolutegravir, Tenofovir, and Emtricitabine as Initial Therapy Despite High-Level Transmitted Multiclass Resistance

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Multiclass high-level transmitted HIV drug resistance is uncommon, and the selection of the optimal initial antiretroviral drug regimen may be challenging. We report a case of extensive transmitted multiclass resistance successfully treated with dolutegravir, tenofovir, and emtricitabine even though the baseline genotype demonstrated full susceptibility to only 1 drug class, integrase strand transfer inhibitors. Our case highlights both the high resistance barrier of dolutegravir and the residual antiviral activity of nucleoside reverse transcriptase inhibitors despite extensive resistance on genotype.

Keywords. HIV; antiretroviral therapy; drug resistance; dolutegravir; integrase strand transfer inhibitor.

Transmitted drug resistance is detected in 10%–20% of newly diagnosed people with HIV [1–3]. Despite this high rate of detected resistance, these findings are generally of little clinical relevance in the current antiretroviral therapy (ART) era and rarely lead to significant difficulty in achieving viral suppression. This is due to the increased utilization of potent, high–resistance barrier integrase strand transfer inhibitors (INSTIs), such as dolutegravir (DTG) and bictegravir (BIC), in combination with 2 nucleoside reverse transcriptase inhibitors (tenofovir plus emtricitabine or lamivudine), and due to the rarity of transmitted INSTI resistance [4, 5]. Therefore, while still recommended in clinical guidelines, baseline resistance testing at diagnosis has not been found to be cost-effective and offers little clinical benefit when evaluating newly diagnosed patients initiating a DTG- or BIC-based 3-drug regimen [6].

In rare cases, newly diagnosed patients with HIV can possess transmitted drug resistance to several antiretroviral classes. These situations may pose significant challenges in the selection of an optimal initial treatment regimen. We describe a person with HIV with extensive transmitted multiclass ART resistance who achieved viral suppression on DTG, tenofovir alafenamide, and emtricitabine. The case highlights the efficacy and the high resistance barrier of DTG even when used as the only fully active drug in a combination regimen and the residual antiviral activity of nucleoside reverse transcriptase inhibitors (NRTIs) despite extensive genotype resistance.

CASE PRESENTATION

A 35-year-old man was diagnosed with HIV in the setting of routine sexual health screening in May 2015. His risk factor for HIV acquisition was sexual intercourse with a partner known to have longstanding HIV. This partner was diagnosed with HIV in 1994 and had extensive antiretroviral treatment experience. The partner's HIV genotype information was not available to our treatment team.

At the time of diagnosis, his HIV viral load was 3600 copies/mL with a CD4 count of 506 (21%). Genotype resistance testing performed at diagnosis (Table 1) demonstrated significant NRTI resistance (M41L, D87N, K70T, L74V, M184V, T215Y, predicted intermediate resistance to tenofovir, high-level resistance to all other NRTIs), non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance (A98G, K103N, L100I, predicted intermediate resistance to etravirine, high-level resistance to all other NNRTIs), and multiple protease inhibitor (PI) mutations (major: V32I, M64I, I47V, I50V, I54M, L90M; minor: L10I, L33F, K43T, A71L; predicted high-level resistance to all PIs). Envelope and INSTI genotypic testing and an HIV tropism assay were obtained after it was found that this patient had extensive multiclass drug resistance on his baseline standard genotype. HIV-1 envelope glycoprotein genotype demonstrated an N42T mutation with predicted resistance to enfuvirtide. There was no genotypic evidence of INSTI resistance at baseline. Co-receptor tropism assay demonstrated a dual/mixed virus population with no predicted CCR5 antagonist activity. Phenotype resistance testing demonstrated predicted resistance to stavudine and zidovudine, partial sensitivity to tenofovir and didanosine, and sensitivity to abacavir, emtricitabine, and lamivudine. Resistance was predicted to all NNRTIs, except for etravirine (partial sensitivity), and to all protease inhibitors.

Given the relatively preserved CD4 cell count and low HIV RNA, he was initially observed off therapy. However, in July

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Table 1. Results of Pretreatment (Baseline) Resistance and Tropism Testing, Demonstrating High-Level Transmitted Resistance to Most Available Drug Classes

ART Class	Mutations	Predicted Resistance
Nucleoside reverse transcriptase inhibitor (NRTI)	M41L, D87N, K70T, L74V, M184V, T215Y	High-level resistance to lamivudine, abacavir, zidovudine, stavudine, didanosine, emtricitabine Intermediate resistance to tenofovir
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	A98G, K103N, L100I	High-level resistance to: efavirenz, nevirapine, rilpivirine Intermediate resistance to etravirine
Protease inhibitor (PI)	Major: V32I, M46I, I47V, I50V, I54M, L90M Minor: L10I, L33F, K43T, A71L	High-level resistance to atazanavir/r, darunavir/r, fosamprenavir/r, indinavir/r, nelfinavir/r, saquinavir/r, tipranavir/r
HIV-1 envelope glycoprotein	N42T	Resistance to enfuvirtide
Integrase strand transfer inhibitor (INSTI)	None	None
Co-receptor tropism assay	Dual/mixed virus population (use CXCR4 and/or CCR6 co-receptors)	No predicted CCR5 antagonist activity

Abbreviation: ART, antiretroviral therapy.

2017 the results of the DAWNING study of DTG vs lopinavir/ritonavir (LPV/r) as second-line therapy were presented for the first time at the annual international AIDS conference (study results were subsequently published) [7]. This study demonstrated that DTG plus NRTIs with at least 1 NRTI with predicted activity by genotypic testing demonstrated high rates of viral suppression. As a result of these findings and the patient's rise in viral load to 8298 copies/mL, in September 2017 he was started on DTG plus tenofovir alafenamide and emtricitabine. He rapidly achieved viral suppression, which was maintained through 48 months of follow-up.

DISCUSSION

All recommended initial regimens for HIV treatment include a second-generation INSTI, DTG or BIC [4]. Compared with their predecessors in the INSTI class, raltegravir (RAL) and elvitegravir, both DTG and BIC demonstrate a higher barrier to resistance manifesting as a lower risk of emergent resistance on treatment failure when used as part of first-line regimens. In treatment-experienced patients, furthermore, the lower resistance barrier of early generation INSTIs in patients with viral suppression was highlighted in the SWITCHMRK study. Individuals with viral suppression on LPV/r were randomized to continue LPV/r or to switch to RAL. The RAL strategy did not meet noninferiority thresholds, with more treatment failure in the RAL arm, with the unfavorable results driven by patients with background NRTI resistance [8]. These results suggest that RAL could not maintain viral suppression reliably without other fully active agents.

The higher resistance barrier of second-generation INSTIs has also been observed to be beneficial in patients with treatment failure. The SAILING study randomized patients with virologic failure and resistance to 2 or more classes of ART to receive either DTG or RAL in combination with up to 2 other antiretroviral medications. DTG was found to be superior to RAL, with significantly fewer cases of virologic failure and treatment-emergent INSTI resistance [9]. This study established DTG as the INSTI of choice for patients with treatment failure and underlying resistance. These findings were subsequently confirmed in the DAWNING and NADIA trials, which demonstrated that DTG was superior (DAWNING) or noninferior (NADIA) to a boosted PI, the previous gold standard for high–resistance barrier therapy [7, 10]. The results of the NADIA trial are particularly notable as several of the study participants had no predicted activity for the tenofovir/lamivudine NRTI pair, and all participants were previously receiving this NRTI combination.

There is relatively little guidance for the management of patients with transmitted multidrug-resistant virus. The initiation of ART should generally not be delayed pending results of genotypic analysis, but in the case described, deferring therapy until this testing returned was reasonable given the high likelihood of baseline high-level resistance. While baseline drug resistance testing has not been shown to be cost-effective in the evaluation of newly diagnosed HIV, our case highlights the potential benefit of genotype testing when transmitted drug resistance is suspected. In addition, it shows that genotype tests are more sensitive than phenotype tests in picking up resistance in the context of viral mixtures, as his phenotype erroneously reported sensitivity to abacavir, emtricitabine, and lamivudine. Furthermore, specific genotype testing for INSTI resistance should be considered in patients with multiclass drug resistance on baseline genotype testing that only includes reverse transcriptase and protease inhibitors. NNRTI and NRTI mutations comprise the majority of transmitted drug resistance, followed by PI resistance [11]. Because transmitted drug resistance to DTG and BIC is rare and the potency of these agents has been well described, these later-generation INSTIs are recommended as part of the initial treatment regimen even for patients with suspected transmitted drug resistance [4, 11, 12]. One caveat is that a 2-drug initial treatment

regimen with DTG/lamivudine should be avoided in patients with suspected transmitted drug resistance until genotype results are available [5].

Given the scarcity of data available at the time of our treatment decision, we extrapolated the results of the DAWNING trial to our treatment-naïve patient with multiclass drug resistance. This study demonstrated high rates of virologic suppression in patients on DTG plus NRTIs, provided at least 1 active NRTI was included in the regimen. In our case, the partially active NRTI was tenofovir alafenamide, though the results of the NADIA study suggest that even if tenofovir activity had not been predicted, the DTG-based regimen would have likely succeeded. The high resistance barrier of DTG and possible residual activity of NRTIs, even in the setting of multiclass resistance, likely explain our treatment success [13, 14]. It is also possible that the patient's relatively low pretreatment viral load contributed to suppression on this regimen. Notably, despite its high resistance barrier, DTG monotherapy is not recommended due to an excess risk of treatment failure and resistance [15].

In summary, we present an unusual case of multiclass transmitted drug resistance successfully treated with DTG plus tenofovir alafenamide and emtricitabine, which is notably a regimen recommended even in the absence of multiclass resistance. Viral suppression was achieved and maintained even though DTG was the only fully active agent in the regimen.

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Patient consent. Our paper does not include factors necessitating patient consent.

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