Open Forum Infectious Diseases

BRIEF REPORT

Virological Failure in HIV to Triple Therapy With Dolutegravir-Based Firstline Treatment: Rare but Possible

M. J. Pena,[1] N. Chueca,[2] A. D'Avolio,[3] J. M. Zarzalejos,[4] and F. Garcia[2]

[1]Servicio de Microbiología, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de GC, Gran Canaria, Spain; [2]Unidad de Gestión Clínica de Microbología, Hospital Universitario San Cecilio, Insituto de Investigación IBS, Granada, Spain; [3]Laboratory of Clinical Pharmacology and Pharmacogenetics, Department of Medical Sciences, University of Turin - ASL "Città di Torino," Torino, Italy; [4]Servicio de Medicina Interna, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Gran Canaria, Spain

We describe a case of virological failure during initial treatment with tenofovir disoproxil fumarate/emtricitabine/dolutegravir twice daily, with concomitant rifampin treatment of staphylococcal infection, selection of R263K + E157Q, and low plasma dolutegravir levels. Using rifampin together with dolutegravir may require closer follow-up, and, if possible, plasma dolutegravir levels should be monitored.

Keywords. dolutegravir; failure; firstline.

Integrase strand inhibitor (INSTI)–based regimens are recommended as firstline treatment for HIV infection by international guidelines [1]. Dolutegravir (DTG), a second-generation INSTI, is commonly prescribed due to its efficacy, once-daily dosing, and high barrier to resistance. Virological failure to DTG-containing triple therapy regimens is a rare event, with only a few cases reported to date in treatment-experienced individuals [2–4]. It is commonly associated with the emergence of an R263K integrase mutation, a substitution that confers low-level resistance to DTG and diminishes HIV DNA integration and viral fitness [5]. No DTG mutations have been reported at 96 or 148 weeks in firstline therapy in clinical trials [6–9]. Here, we describe a case of virological failure during initial treatment with tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), and DTG associated with resistance selection at position 263, in the context of high viral replication capacity.

CASE REPORT AND RESULTS

A 49-year-old woman was diagnosed with HIV-1 infection during hospital admission for lumbar spine surgery. At diagnosis (w0), her CD4 count was 39 cells/μL, her plasma HIV-1 RNA was 457 000 copies/mL, and Sanger sequencing detected no reverse transcriptase (RT), protease, or integrase mutations. Her body mass index (BMI) was 16.81, and no deficiency in relation to drug metabolism was reported. The patient started treatment with trimethoprim-sulfamethoxazole (TMP/STX) 800/160 mg/d. Antiretroviral treatment (ART) was started 1 week later with TDF/FTC and DTG 50 mg twice daily (BID), as she was taking rifampin (600 mg/d) for a staphylococcal infection at the surgical site. Two weeks after ART initiation (w2), TMP/STX was replaced with levofloxacin (750 mg/d) and pentamidine (300 mg/mo) because of a hypersensitivity reaction. The patient was discharged from hospital at week 3; a week later (w4), her viral load (VL) was 3461 copies/mL, and her CD4 had increased to 113 cells/μL. At w8, rifampin was withdrawn because of a cutaneous adverse reaction, and valganciclovir (450 mg/12h) was added due to elevated liver enzymes and cytomegalovirus viremia. After a 14-day rifampin washout, DTG was given once daily (QD). The patient was diagnosed with Norwegian scabies, and ivermectin (6 mg/wk) was added to her medication. At w12, her CD4 count was 42 cells/μL, and her VL had increased to 126 393 copies/mL. Adherence was confirmed both by hospital records (directly observed ART during admission) and patient interview, and virological failure was confirmed in a second sample (w14; VL 208 518 c/mL). Sanger sequencing performed at w14 revealed the presence of M184V in RT and R263K in the integrase. Treatment was switched to TDF, darunavir/cobicistat, and rilpivirine (RPV), and her VL decreased thereafter to 3148 copies/mL (w18), 595 copies/mL (w22), and 25 copies/mL (w30); at her final check-up at w44, the VL was undetectable, and her CD4 count was 305 cells/μL. We retrospectively analyzed stored samples using deep sequencing (2% cutoff): no resistance mutations were detected in the RT, protease, or integrase at baseline. Deep sequencing showed the sequential emergence of M184I (40%, w4; 42% w12; 14% w14) in RT, which began to be replaced by M184V at w12 (57%) and w14 (86%). Interestingly, R263K was detected at a very high prevalence (>97%) at weeks 12, 14, and 18 and was accompanied by the emergence of E157Q (4%, w12; 8%, w14; 20%, w18) in the integrase gene. As expected, both E157Q and R263K were linked in the same quasispecies. Deep sequencing of *pol* and *env* revealed infection by a circulating recombinant form (CRF14_BG). Plasma DTG levels were also retrospectively analyzed, finding 401 ng/mL at w4 and 696 ng/mL at w12 (in vitro reference value, 640 ng/

Received 16 October 2018; editorial decision 24 November 2018; accepted 5 December 2018 ; published online December 10, 2018.

Correspondence: F. García, PhD, Avda de la Innovación S/N. 18008. Granada, Spain (fegarcia@ugr.es).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofy332

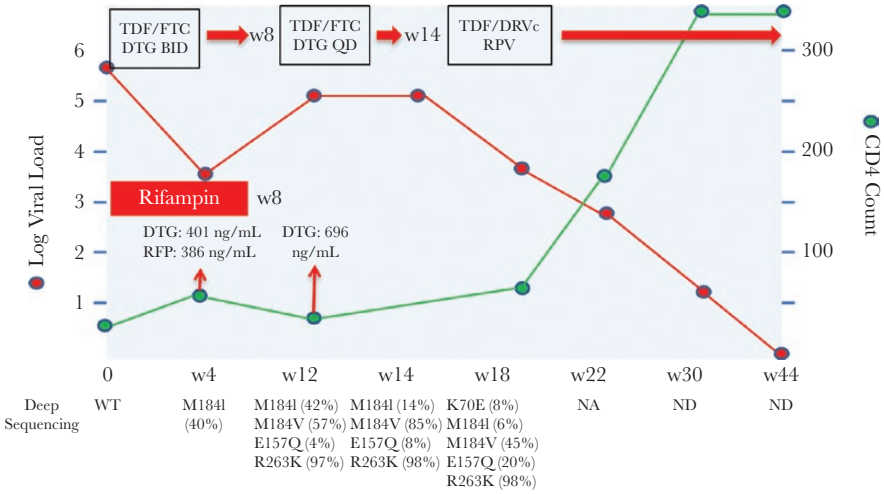

Figure 1. Virological and immunological evolution of the patient since initiation of antiretroviral treatment. Dolutegravir levels are considered appropriate when they are above 640 ng/mL. Viral load is expressed as log RNA copies/mL; CD4 count is expressed as cells/μL. Abbreviations: BID, twice daily; DRVc, darunavir cobicistat; DTG, dolutegravir; FTC, emtricitabine; QD, once daily; RFP, rifampin; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.

mL). Rifampin levels at w4 were 386 ng/mL (reference range, 8000–24 000 ng/mL after 2 hours [Tmax]). The case report is summarized in Figure 1.

DISCUSSION

Here we present one of the first reports of treatment failure to a DTG-containing firstline regimen, with the selection of an R263K integrase mutation, together with unexpected high viral fitness. Using deep sequencing, we were able to trace the development and replacement of mutations. Interestingly, we have shown for the first time in vivo that E157Q restores viral fitness in R263K-containing viruses. Although the patient was treated with DTG BID, we found unexpectedly low plasma levels while she was taking rifampin. We hypothesize that functional bi-therapy with TDF/FTC led to the selection of M184I, and viral evolution led to integrase failure through the R263K pathway, together with a very high fitness cost compensation by E157Q, which has so far only been described in vitro [10].

Lübke et al. [11] recently reported DTG treatment failure in a subtype F–infected patient with very advanced HIV disease at presentation (22 CD4 cells/μL; 1.4×10^6 HIV-RNA copies/mL) admitted to hospital with tuberculosis and pericarditis. Concomitant to the tuberculosis treatment with rifabutin, ethambutol, isoniazide, and pyrazinamide, the patient had been treated with TDF/FTC/DTG for 8 months when analysis showed M184V in RT and R263K and G118R in integrase. Retrospective deep sequencing on stored samples revealed initial detection of M184V and R263K together at w14, with the addition of G118R at w26. As in our case, the patient was successfully suppressed using TDF/FTC, RPV, and boosted darunavir; however, in contrast, the DTG levels were always above Cmin values, the selected viruses were less fit, and R263K and G118R were apparently not linked in the same quasispecies, which is consistent with different resistance pathways. The authors suspected lack of adherence to the antiretroviral regimen as the most likely explanation for the viral failure.

Fulcher et al. [12] also reported early virological failure to TDF/FTC/DTG, again in a severely immunocompromised patient (78 CD4 cells/μL; 1.9×10^6 HIV-RNA copies/mL) infected at baseline by a wild-type virus in the RT and protease (standard population sequencing). After an initial viral response, the VL increased to 15 700 copies/mL at day 27, and standard sequencing revealed M184V in RT and G163E in the integrase. After adding boosted darunavir to the regimen, and a later switch to RPV, the patient was virologically suppressed for >2 years. Retrospective deep sequencing in a partial portion of the integrase revealed a wild-type virus before day 27, rapid selection of I151V-G163E (34.5%) also by day 27, and the addition of Q148R (20.9%) 5 days later. Unlike our study and the prior study by Lübke et al., no DTG levels were available, and only a partial fragment of the integrase gene could be studied, so the presence of R263K could not be ruled out.

Lepik et al. [13] previously described how a CD4 count <200 cells/μL and viremia >100 000 HIV-RNA copies/mL were highly associated with emergent resistance to INSTI-based regimens. As in the other 2 cases [11, 12], our patient was diagnosed at a highly advanced HIV stage. In this case, we report very early selection of M184I, which was not found at baseline by deep sequencing with a 2% cutoff, and quick replacement by M184V, before the development of INSTI resistance. We hypothesize that M184V emerged in the context of suboptimal DTG levels and contributed to the rapid selection of resistance.

We believe that the key issue for virological failure was the unexpectedly low DTG levels while the patient was taking the

drug BID. Although rifampin lowers DTG levels (54%, area under the curve [AUC]; 72%, Cmin; www.hiv-druginteractions.org), which may be extremely important for patients with concomitant tuberculosis treatment, the safety and efficacy of DTG BID and rifampin have already been proven [14]. In our patient, we were unable to find any factor that might clearly explain the decreased DTG levels while taking the drug BID. The patient was hospitalized during the first 3 weeks of treatment, and medication was administered under direct observation, so, although possible, it seems unlikely that a lack of adherence during the following week, when she was discharged from hospital, could be responsible for a drop in DTG levels and the selection of M184I. None of the drugs that were concurrently administered with DTG have been reported to lower DTG plasma levels, and no metabolism deficiency was recorded. However, decreased drug absorption due to the patient's low BMI cannot be ruled out. Rifampin washout was performed according to clinical recommendations before switching to DTG once daily, but drug levels continued to be borderline according to the recommended DTG concentration (640 ng/mL), which could certainly contribute to viral evolution. Although our patient was infected by a recombinant non-B subtype, where baseline polymorphisms are more frequent, HIV-clade has not been associated with a different INSTI resistance pattern, even if Q148 + G140 mutations have been more frequently observed in HIV-B clades [15]; however, even with boosted darunavir + tenofovir and RPV, it took 22 weeks to fully suppress the patient, suggesting that the immunological response may have been affected.

In summary, we describe a case of virological failure during initial treatment with DTG BID, with concomitant rifampin use, and unexpectedly low plasma DTG levels. After early detection of M184I, unexpected selection of a highly fit virus with R263K in the integrase and the compensatory E157Q mutation was found. We believe that this case may serve to alert clinicians that the use of rifampin as treatment for staphylococcal infection together with DTG BID may require closer follow-up, and, if possible, plasma levels should be monitored.

Acknowledgments

We acknowledge Drs. Romina Quercia and Luis Ramos for personal discussion and Jose Angel Fernández-Caballero for technical assistance with deep sequencing.

Funding. This work was supported by Plan Nacional de I+D+I and Fondo Europeo de Desarrollo Regional-FEDER (RD16/0025/0040) and Fundación Progreso y Salud, Junta de Andalucia (PI-0550-2017).

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. **2016**. http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1. Accessed 13 November 2018.
2. Cahn P, Pozniak AL, Mingrone H, et al; extended SAILING Study Team. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet **2013**; 382:700–8.
3. Aboud M, Brites C, Lu H, et al. DTG versus LPV/R in second line (DAWNING): outcomes by WHO-recommended NRTI backbone. Top Antivir Med **2018**; 26:40–53.
4. Cardoso M, Baptista T, Diogo I, et al. Two cases of dolutegravir failure with R263K mutation. AIDS **2018**; 32:2639–40.
5. Mesplède T, Leng J, Pham HT, et al. The R263K dolutegravir resistance-associated substitution progressively decreases HIV-1 integration. MBio **2017**; 8:e00157–17.
6. Clotet B, Feinberg J, van Lunzen J, et al; ING114915 Study Team. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet **2014**; 383:2222–31.
7. Raffi F, Jaeger H, Quiros-Roldan E, et al; extended SPRING-2 Study Group. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis **2013**; 13:927–35.
8. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet **2017**; 390:2073–82.
9. Walmsley SL, Antela A, Clumeck N, et al; SINGLE Investigators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med **2013**; 369:1807–18.
10. Anstett K, Cutillas V, Fusco R, et al. Polymorphic substitution E157Q in HIV-1 integrase increases R263K-mediated dolutegravir resistance and decreases DNA binding activity. J Antimicrob Chemother **2016**; 71:2083–8.
11. Lübke N, Jensen B, Hüttig F, et al. Failure of dolutegravir-containing first-line regimen. Paper presented at: 16th European Meeting on HIV & Hepatitis; 30 May–1 June **2018**; Rome, Italy.
12. Fulcher JA, Du Y, Zhang TH, et al. Emergence of integrase resistance mutations during initial therapy containing dolutegravir. Clin Infect Dis **2018**; 67:791–4.
13. Lepik KJ, Harrigan PR, Yip B, et al. Emergent drug resistance with integrase strand transfer inhibitor-based regimens. AIDS **2017**; 31:1425–34.
14. Dooley K, Kaplan R, Mwelase T, et al. Safety and efficacy of dolutegravir-based ART in TB/HIV co-infected adults at week 48. Paper presented at: 22nd International AIDS Conference; 23–27 July **2018**; Amsterdam.
15. Fourati S, Charpentier C, Amiel C, et al; ANRS AC11 Resistance Study Group. Cross-resistance to elvitegravir and dolutegravir in 502 patients failing on raltegravir: a French national study of raltegravir-experienced HIV-1-infected patients. J Antimicrob Chemother **2015**; 70:1507–12.