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PERSPECTIVES

Emergent Resistance to Dolutegravir Among INSTI-Naïve Patients on First-line or Second-line Antiretroviral Therapy: A Review of Published Cases

Muge Cevik,[1,2] Chloe Orkin,[3,4] and Paul E. Sax[5,6]

[1]Infection and Global Health Research, School of Medicine, University of St Andrews, St Andrews, UK, [2]NHS Lothian Infection Service, Specialist Virology Laboratory, Royal Infirmary of Edinburgh, Edinburgh, UK, [3]Blizzard Institute, Queen Mary University of London, London, UK, [4]Royal London Hospital, Barts Health NHS Trust, London, UK, [5]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts, USA, and [6]Harvard Medical School, Boston, Massachusetts, USA

None of the licensing studies of dolutegravir (DTG) reported any treatment-emergent resistance among DTG-treated individuals, though virological failure in treatment-naïve and treatment-experienced, integrase strand transfer inhibitor (INSTI)–naïve individuals has been reported in clinical practice. While the spectrum of dolutegravir-selected mutations and their effects on clinical outcome have been described, the clinical characteristics of these rare but important virological failure cases are often overlooked. In this perspective piece, we focus on key clinical aspects of emergent resistance to DTG among treatment-naïve and treatment-experienced INSTI-naïve patients, with an aim to inform clinical decision-making. Poor adherence and HIV disease factors contribute to emergent drug resistance, even in regimens with high resistance barriers. Patients with severe immunosuppression or poor adherence are under-represented in licensing studies, and these patients may be at higher risk of treatment failure with DTG resistance, which requires close clinical and laboratory follow-up.

Keywords. dolutegravir; HIV; treatment failure; treatment-naïve; resistance.

Multiple international guidelines recommend dolutegravir (DTG)-based antiretroviral therapy as a preferred first- and second-line treatment regimen for HIV-1, a shift prompted by the efficacy, safety, and resistance barrier of DTG. Although the spectrum of dolutegravir-selected mutations and their effects on clinical outcome have been described [1], the clinical characteristics of rare but important virological failure cases are often overlooked. This perspective piece will particularly focus on key clinical aspects of emergent resistance to DTG among treatment-naïve and treatment-experienced integrase strand transfer inhibitor (INSTI)–naïve patients, with an aim to inform clinical decision-making.

TREATMENT-NAÏVE INDIVIDUALS

In total, we identified 5 VF cases (Table 1). In a retrospective cohort study of patients starting or switching to an INSTI-containing regimen, 1 VF case was described out of 58 patients starting DTG-based therapy; this person had virological rebound at 11 months after a period of viral suppression, associated with emergent T66I [2]. Although no pharmacokinetic (PK) data were available, poor adherence was reported. In the ACTG 5353 trial, 3 participants out of 120 on DTG and lamivudine (3TC) had VF [3]. One participant experienced viral rebound at week 8 after an initial response at week 4, followed by prolonged viremia; M184V and R263R/K emerged at week 14. The virological rebound was linked to very poor adherence and possible intermittent monotherapy, with undetectable DTG levels.

In the remaining 3 case reports, DTG resistance is reported in patients with excellent reported medication adherence, all of whom had advanced HIV disease and active co-infections. Fulcher et al. reported a virological failure (VF) in a severely immunosuppressed patient with *Pneumocystis jirocecii* pneumonia (PCP) who was admitted to intensive care [4]. After a decline in HIV viral load (VL) to 2770 copies/mL at week 2, the VL increased to 6510 copies/mL and then 15 700 copies/mL at days 23 and 27, respectively, despite full adherence throughout the hospital stay. Deep sequencing of reverse transcriptase (RT) and integrase (IN) gene amino acid region 142–165 revealed M184V and a selection of I151V-G163E followed by the emergence of Q148R. The patient subsequently achieved virologic suppression on tenofovir alafenamide (AF)/emtricitabine/rilpivirine/DTG. Pena et al. [5] reported VF in a severely immunosuppressed patient diagnosed with HIV while in the hospital for spinal surgery subsequently complicated by *Staphylococcus aureus* infection requiring rifampicin. After an initial VL decline to

Received 17 January 2020; editorial decision 26 May 2020; accepted 28 May 2020.

Correspondence: M. Cevik, MD, MSc, MRCP(UK), Division of Infection and Global Health Research, School of Medicine, University of St Andrews, Fife, KY16 9TF (mc349@st-andrews.ac.uk).

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DOI: 10.1093/ofid/ofaa202

Table 1. Summary of DTG Failure Cases With Emergent DTG Resistance Mutations

Studies Reported	Age, y	Baseline VL, Copies/mL	Nadir CD4, Cells/μL	Active Infection	ARVs	Conmeds	DTG PK	Time to RAM Emergence	Hospital Discharge to ART Initiation	Resistance Mutation
Treatment-naïve										
Lepik [2]	50–60	260 000	430	Not known	DTG OD ABC-3TC	Not known	N/A	Week 46	Outpatient	T66I
Taiwo [3]	<50	~70 000	>200	-	DTG OD 3TC	No conmeds	DTG levels below the in vitro inhibitory concentration for 90% inhibition (IC_{90}; 64 ng/mL) at weeks 8 and 24	Week 14	Outpatient	R263R/K M184V
Fulcher [4]	46m	1 970 000	78	PCP BAL+	DTG OD TDF-FTC	Cotrimoxazole Prednisolone	Not performed	Week 4	Week 5	Q148K I151V-G163E M184V
Pena [5]	49f	457 000 non-B subtype	38	Staphylococcal infection post– spinal surgery CMV viremia Norwegian scabies	DTG 50 mg BD TDF-FTC	Trimethoprim-sulfamethoxazole Rifampin Ivermectin Levofloxacilin Pentamidine Valganciclovir	DTG levels 401 and 696 ng/mL at w4 and w12, respectively (paEC90, 640 ng/mL)	Week 14	Week 3	R263K E157Q M184V
Lubke [6]	27m	1 400 000 subtype F	22	Disseminated MTB	DTG OD TDF-FTC	Rifabutin Ethambutol Isoniazid Pyrazinamide Prednisolone	DTG levels below the mean reference trough levels (Cmin; 1110 ng/mL) at weeks 3 and 26	Week 8	Week 3	R263K G118R M184V
Treatment-experienced, INSTI-naïve										
Aboud [7]		>100k		Not known	DTG OD + FTC (inactive) + TDF		N/A	Week 48	Outpatient	G118R Asp67Asn
Aboud [7]		>100k		Not known	DTG OD + 3TC (inactive) + AZT		N/A	Week 36		His51His/Tyr; G118R Glu138Glu/Lys Arg263Arg/Ls
Cahn [8]		5 log 10		Not known	DTG OD + TDF + DRV/r		N/A	Week 16		R263R/K
Cahn		N/A		Not known	DTG OD + TDF + FTC		N/A	N/A		V260I R263R
Cahn		>100k		Not known	DTG OD + ABC + 3TC		DTG below the level of detection (LOD = 0.002 mg/mL)	Week 108		N155H
Cahn		>100k		Not known	DTG OD + TDF + DTV/r		Documented noncompliance	Week 72		N155H
Cahn		<1000 copies/mL		Not known	DTG OD + TDF + FTC		DTG = 0.003 mg/mL (just above LOD)	Week 120		R263K
Vavro [10]	12	>10k		Not known	DTG OD + FTC + TDF		Noncompliance	Week 32		R263K
Vavro	16	>10k		Not known	DTG OD + EFV + FTC + TDF		Off treatment for 5 mo	Week 192		G118R

Table 1. Continued

Studies Reported	Age, y	Baseline VL, Copies/mL	Nadir CD4, Cells/μL	Active Infection	ARVs	Conmeds	DTG PK	Time to RAM Emergence	Hospital Discharge to ART Initiation	Resistance Mutation
Vavro	7	>100k		Not known	DTG OD + 3TC + AZT		Noncompliance	Week 48		G118R E138E
Lepik [2]		<50	>200	Not known	DTG OD ABC-3TC	Not known	Poor compliance	Week 38		R263K
Lepik		10–100k	>200	Not known	DTG OD ABC-3TC	Not known	Poor compliance	Week 24		R263K

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ARVs, antiretrovirals; AZT, Zidovudine; BAL, Bronchoalveolar lavage; CMV, Cytomegalovirus; DTG, dolutegravir; EFV, Efavirenz; FTC, Emtricitabine; INSTI, integrase strand transfer inhibitor; LOD, limit of detection; MTB, Mycobacterium tuberculosis; OD, once-daily; PCP, *Pneumocystis jirocecii* pneumonia; PK, pharmacokinetic; RAM, resistance-associated mutations; TDF, Tenofovir disoproxil fumarate; VL, viral load.

3461 copies/mL at week 4, VF was confirmed at week 12 with a VL of 126 393 copies/mL. Deep sequencing revealed M184V at week 4, followed by R263K plus M184V and subsequent evolution of E157Q. Despite receiving 50 mg BD with concomitant rifampicin, DTG plasma levels were below the expected in vitro protein-adjusted 90% inhibitory concentration IC_{90} of 64 ng/mL at week 4. The patient achieved virologic suppression on tenofovir DF, darunavir/cobicistat, and rilpivirine. Lubke et al. reported another VF in a severely immunosuppressed patient with disseminated tuberculosis [6]. Treatment included rifabutin, so DTG was dosed once daily. The patient had a 3-log viral load decline in the first 3 weeks; however, postdischarge, they experienced viral rebound at week 8 and subsequently had persistent 10^3-copies/mL viremia. Deep sequencing revealed the evolution of R263K at week 8 and G118R by week 15. Suboptimal DTG levels were recorded despite good reported adherence.

TREATMENT-EXPERIENCED INSTINAÏVE PATIENTS

We Identified 10 VF Cases With Emergent DTG Resistance

Among 627 patients in the DAWNING trial, 312 patients were randomized to dolutegravir. Among those 2 with baseline NRTI resistance mutations developed VF with INSTI resistance mutations (0.6%) (Table 1) [7]. Both had >100k viral load at the time of ART initiation, and VF was observed at weeks 48 and 36 with G118R.

In the SAILING trial, of the 715 patients randomized, 5 individuals on dolutegravir developed VF with INSTI resistance mutation [8]. Two individuals (0.6%) developed 1 or more INSTI resistance mutations by week 48. One patient had fluctuating HIV-RNA after week 4 despite being on DTG plus Tenofovir disoproxil fumarate (TDF) and darunavir/r and developed R263K substitution. Another 3 (0.8%) patients developed mutations after week 48. Of those, 2 had baseline VL >100k copies/mL. The first patient had a DTG trough level below the limit of detection at week 24 and experienced VF at week 108 with emergent N155H. The second patient had documented noncompliance and developed VF at week 72 with emergent N155H, I60L, and T97A. Both had a loss of M184V. The third patient had a baseline VL <1000 copies/mL, showed a gradual VL increase from week 96 to week 132, and developed emergent R263K.

In the IMPAACT P1093, heavily treated children aged 12–18 were given weight-based dolutegravir [9]. Of the initial 23 recruited, 1 developed emergent INSTI resistance. A subsequent analysis of 38 adolescents identified 2 additional cases of VF with emergent INSTI resistance. All 3 cases had documented noncompliance before developing VF [10].

In the Lepik et al. study, VF with emergent INSTI resistance was observed in 2 patients. Both were on DTG with Lamivudine (3TC) and abacavir (ABC) and had baseline CD4 counts >200; 1 had HIV RNA <50, and the other had VL 1-100.000 copies/mL. Both had lower than optimum compliance and developed VF at week 38 and week 24 with emergent 263K [2].

DISCUSSION

We reviewed relatively rare but important cases of treatment failure with emergent DTG resistance. Clinically important risk factors for the development of resistance include poor medication adherence, drug interactions, and HIV disease factors, in particular, high baseline VL and active opportunistic infections.

Of the 15 cases, 10 had either suboptimal DTG levels when they were measured or had documented poor adherence, and 3 had advanced HIV and severe active infections. Factors such as malabsorption could influence the plasma PK of antiretrovirals (ARVs) in severely immunosuppressed HIV patients [11–13]. Drug absorption in critically ill patients may be impaired [14]. Administration of drugs through enteral feeding tubes

can decrease DTG drug absorption [15]. Although the efficacy of twice-daily DTG dosing with rifampicin and once-daily dosing with rifabutin is considered sufficient [16, 17], drug interactions may play an important role. These observations highlight that critically ill individuals with concurrent AIDS-defining active infection or individuals with poor adherence require closer follow-up.

In addition, 4 treatment-naïve and 5 treatment-experienced patients had a baseline VL >100 000 copies/mL, which has been associated with treatment failure in some studies with INSTI-based regimens [2, 18]. In GEMINI and NAMSAL [19, 20], CD4s <200 Cells/μL and VLs >100k copies/mL, respectively, had more virologic failure, whereas Lepik et al. [9] demonstrated an association with emergence of resistance. The lack of viral load or genotypic testing, especially, may influence the proportion of persons with VF and emergent INSTI resistance in low- and middle-income countries.

These findings also have some implications for bictegravir (BIC) use. Lozano et al. described a VF case on bictegravir/emtricitabine/tenofovir alafenamide in an INSTI-experienced patient with a long history of noncompliance [21]. After a period of loss to follow-up, this case presented with cerebral toxoplasmosis and a VL of >1 million copies/mL and CD4 of 37 cells/mL. Although the VL dropped to 1084 copies/mL following 4 weeks of bictegravir/emtricitabine/tenofovir alafenamide, the patient developed PML, during which ART was given via an nasogastric (NG) tube for 6 weeks. VF with VL of >10 000 copies/mL was developed, with emergence of M184V and R263K. Two additional cases of virologic failure with resistance have been reported on bictegravir-based regimens, 1 R263K and R138K selection after switching from TDF/FTC/elvitegravir/cobicistat and another with the addition of A256V, a novel mutation in integrase gene (unpublished results).

Transmission of INSTI resistance mutations of clinical significance remains a very rare event—in 1 recent series, it was found in 2/4631 individuals, and neither had DTG or BIC resistance [22].

In conclusion, poor adherence and HIV disease factors may contribute to emergent drug resistance, even in regimens with high resistance barriers such as those including dolutegravir. Patients with severe immunosuppression or poor adherence are under-represented in licensing studies, and these patients may be at higher risk of treatment failure with DTG resistance, which requires close clinical and laboratory follow-up.

Acknowledgments

We thank the corresponding authors of Lepik et al. and Taiwo et al. for providing further information regarding the cases reported.

Financial support. No funding was received.

Potential conflicts of interest. M.C. has no conflicts to disclose. C.O. has received honoraria from, received fees for lectures from, and served on advisory boards for Gilead, MSD, Viiv, and Janssen. She has also received research grants to her institution from the above-mentioned companies. P.E.S. has received honoraria from, received fees for lectures from, and served on advisory boards for Gilead, Merck, Janssen, and ViiV; he has also received research grants to his institution from Gilead and ViiV.

Author contributions. M.C., C.O., and P.E.S. conceptualized this commentary, M.C. collated the data and drafted the first manuscript, and all authors substantially contributed to the final manuscript.

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