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BRIEF REPORT

Clinical Features and Outcomes of Bloodstream Infections Caused by New Delhi Metallo-β-Lactamase–Producing *Enterobacterales* During a Regional Outbreak

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Limited data about New Delhi metallo-β-lactamase (NDM) bacteremia are available. Blood isolates from 40 patients with NDM bacteremia were studied for antibiotic susceptibility and whole-genomic sequencing. NDM bacteremia has high 30-day mortality. In most cases, aztreonam-avibactam is active in vitro. Ceftazidime-avibactam plus aztreonam may represent a feasible therapeutic option.

Keywords. bacteremia; carbapenem-resistant; New Delhi metallo-β-lactamases.

An outbreak of New Delhi metallo-β-lactamase (NDM)–producing *Enterobacterales* was recently documented in the northwestern area of Tuscany [1]. From November 2018 to May 2019, colonization or infection by NDM-producing *Enterobacterales* was documented in 350 patients from 9 different hospitals [1]. We retrospectively reviewed the clinical and microbiological characteristics of 40 patients with documented bloodstream infection (BSI).

METHODS

Cases of NDM-producing BSI were identified by reviewing records from the microbiology laboratories of all 9 institutions. Demographics, clinical and laboratory findings, comorbid conditions, source of infection, source control data, treatment regimens, and 30-day mortality rates were collected from clinical charts. Source of infection and source control were defined as previously described [2]. Septic shock was defined according to the Sepsis-3 definition [3]. The study was approved by the local ethical committee.

Blood isolate identification and susceptibility testing were performed by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-ToF MS; Vitek MS, bioMérieux; or MALDI Biotyper, Bruker Daltonics). Carbapenemase determinants were evaluated by either the Allplex Entero-DR Assay (Seegene) or RESIST-3 O.K.N. ICT immunocromatographic assay (Coris BioConcept, Gembloux, Belgium) and confirmed by real-time polymerase chain reaction as previously described [4]. Antimicrobial susceptibility testing was carried out with reference broth microdilution, except agar dilution for fosfomycin, according to the ISO 20776-1:2006 guidelines [5], and interpreted according to the EUCAST clinical breakpoints (v.9.0 2019; http://www.eucast.org/clinical_breakpoints/).

Isolates were subjected to whole-genome sequencing (WGS) with an Illumina MiSeq platform (Illumina Inc., San Diego, CA, USA) and a paired-end approach (2 × 300 bp). Raw sequences were assembled using SPAdes software [6]. In silico analyses using draft-assembled genomes were performed by dedicated tools available at http://www.genomicepidemiology.org/ (eg, MLST v.2.0) and by the BLAST suite (https://blast.ncbi.nlm.nih.gov/Blast.cgi).

Continuous variables were reported as medians and interquartile ranges (IQRs). The Mann-Whitney *U* test was used to analyze non–normally distributed data. Categorical data were expressed as frequency distributions, and the chi-square test or Fisher exact test was used to determine if differences existed between groups. Factors influencing 30-day survival were examined by univariate analysis. All significant variables at univariate analyses ($P < .05$) were considered for the multivariate model. Hazard ratios (HRs) and 95% confidence intervals (95% CI) were calculated. Statistical significance was established at $P \leq .05$.

RESULTS

Overall, during the study period, 47 patients with BSI caused by NDM-producing strains were initially identified in 9 hospitals in the northwestern area of Tuscany (Italy). Of these, 44 patients

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had a confirmed BSI caused by an NDM-producing strain, whereas 3 patients had an infection caused by strains with a different mechanism of carbapenem resistance (these cases were excluded from further analysis); the data of 4 patients were unavailable. Thus, the final cohort included 40 patients, while 35 strains were available for full microbiological and molecular characterization.

The isolates from bacteremia were identified as *Klebsiella pneumoniae* (31 patients) and *Escherichia coli* (4 patients). Preliminary characterization by WGS revealed that most *K. pneumoniae* isolates belonged to the same clonal lineage, namely sequence type (ST) 147 (n = 30, 96.8%), with a singleton of ST307. The *E. coli* isolates belonged to 2 different clonal lineages, ST8 (n = 2) and ST2 (n = 2). Among the *K. pneumoniae* isolates, all those of ST147 carried the $bla_{\text{NDM-1}}$ gene, whereas those of ST307 carried $bla_{\text{NDM-5}}$ (as did the 4 *E. coli* isolates). All *K. pneumoniae* isolates and the 2 ST8 *E. coli* additionally carried the $bla_{\text{CTX-M-15}}$ extended-spectrum β-lactamase (ESBL) gene. A clonal analysis, based on single nucleotide polymorphisms (SNPs) evaluated on the core genome, revealed that all the ST147 isolates were closely related to each other (SNP range, 0–25), strongly suggesting that the outbreak was due to clonal expansion of a single NDM-1-producing *K. pneumoniae* strain.

Susceptibility patterns determined in vitro for the 35 characterized isolates are detailed in Table 1. All *K. pneumoniae* strains (n = 31) were resistant to expanded-spectrum cephalosporins, carbapenems, and β-lactamase inhibitor combinations, while they were susceptible to aztreonam (ATM)-avibactam (AVI; MIC ≤ 1 mg/L). The *E. coli* isolates (n = 4) showed a similar broad spectrum of β-lactam resistance, but they were more frequently resistant to ATM-AVI, with some differences between the ST8 (n = 2) and ST2 (n = 2) isolates: Whereas the former showed high-level resistance to ATM (MIC > 32 mg/L) and were resistant to ATM-AVI (MIC, 8 mg/L), the latter showed a lower resistance level to aztreonam (MICs, 2 and 8 mg/L) and were not frankly resistant to the AZT-AVI combination (MICs, 2 and 4 mg/L, respectively). Beyond AZT-AVI, the most active antibiotics were colistin and fosfomycin (susceptibility rate of 91.4% and 80.6%, respectively). Almost all strains (97.2%) were resistant to aminoglycosides.

The clinical characteristics of the patient population and comparison between survivors and nonsurvivors are illustrated in Table 2. Half of the bacteremic patients were cared for in medical wards, and 47.5% had malignancy. The majority of patients (67.5%) had previous documented rectal NDM colonization. The overall 30-day mortality rate was 42.5%. Septic shock occurred in 32.5% of patients. The median age and Charlson comorbidity index score were significantly higher in nonsurviving patients than in those who survived. At the same time, primary bacteremia (unknown focus) was more common among patients who died, whereas central venous catheter (CVC)–related bacteremia was more common among survivors.

The most common regimens were ceftazidime-avibactam (CAZ-AVI) plus ATM (30%), followed by a colistin-based regimen (22.5%). In patients treated with CAZ-AVI plus ATM, CAZ-AVI was administered at the dosage of 2.5 g every 8 hours (in 3 patients in continuous infusion) and ATM at the dosage of 2 g every 8 hours. Dosages were eventually adjusted according to renal function. Among 26 patients (65%) receiving an antibiotic regimen showing in vitro activity against the isolated pathogen, the mortality rate was 30.8% (8/26), whereas patients who did not receive any active antibiotic therapy (n = 14, 35%) had a mortality rate of 64.3% (9/14, $P = .041$). Two patients treated with the combination of CAZ-AVI plus ATM died: 1 patient had multiple comorbidities, a severe cardiac dysfunction, and developed septic shock at time of diagnosis, while the other was an intensive care unit (ICU) patient with acute cerebral hemorrhage who was unresponsive to surgical therapy. In no cases was development of resistance to ATM-AVI detected in vivo. Time to death (IQR) was 8 (1–18.5) days in those who received in vitro active therapy, compared with 6 (1–8) days in patients who did not ($P = .481$). Cox regression analysis identified Charlson comorbidity index score (hazard ratio [HR], 1.221; 95% confidence interval [CI], 1.022–1.459; $P = .028$) and age (HR, 1.040; 95% CI, 1.012–1.079; $P = .038$) as factors independently associated with 30-day mortality.

DISCUSSION

This is the first European report on a relatively large group of patients with bacteremia caused by NDM-producing *Enterobacterales*.

A preliminary genomic characterization of isolates revealed that the majority of episodes of BSI were caused by an NDM-1-producing strain of *K. pneumoniae* belonging to ST147. Clonal expansion, therefore, appears to be the major mechanism underlying the large outbreak of NDM-producing strains ongoing in this area, although further characterization of other isolates will be necessary to confirm the contribution of this clone and the diversity of circulating strains.

In the Tuscany cluster, BSIs caused by NDM-producing strains involved patients frequently cared for in medical wards, with multiple comorbidities and severe underlying diseases (such as cancer), and were associated with a high 30-day mortality rate. Mortality was greatly influenced by advanced age and by comorbid conditions, calculated by the Charlson comorbidity index. Moreover, mortality was significantly higher among patients not receiving an in vitro active antibiotic therapy. This latter finding underlines the importance of early detection of the molecular mechanism underlying the carbapenem resistance phenotype; it is noteworthy that some patients who died, according to previous local epidemiological data showing a predominance of KPC-producing strains, were empirically treated with CAZ-AVI alone or in combination with aminoglycosides [7].

Table 1. In Vitro Susceptibilities of 35 NDM-Producing Isolates Collected From Patients With BSI Admitted to 9 Hospitals Across Tuscany in 2018–2019

Bacterial Species (Isolate No.) and Antimicrobial Agent Tested	MIC, mg/L	Susceptibility Rates, %		
	Range	S	I	R
Klebsiella pneumoniae (n = 31)				
Ceftriaxone	>4	-	-	100
Ceftazidime	>64	-	-	100
Cefepime	>16	-	-	100
PIP-TAZ	>128/4	-	-	100
Ciprofloxacin	>1	-	-	100
Levofloxacin	>8	-	-	100
Amikacin	>32	-	-	100
Gentamycin	≤0.5 to >8	3.2	-	96.8
Meropenem	4 to 64	-	3.2	96.8
Ertapenem	1 to >2	-	-	100
TMP-SMX	≤1/19 to >8/152	3.2	-	96.8
Tigecycline	≤0.25 to >4	80.6	-	19.4
Colistin	≤0.5 to >8	90.3	-	9.7
Aztreonam	>32	-	-	100
Fosfomycin[a]	4 to 64	80.6	-	19.4
CLZ-TAZ	>64/4	-	-	100
CAZ-AVI	>32	-	-	100
MER-VAB	4 to >64	3.2	-	96.8
AZT-AVI	≤0.25 to 1	100	-	-
Escherichia coli (N = 4)				
Ceftriaxone	>4	-	-	100
Ceftazidime	>64	-	-	100
Cefepime	>16	-	-	100
PIP-TAZ	>128/4	-	-	100
Ciprofloxacin	>1	-	-	100
Levofloxacin	>8	-	-	100
Amikacin	>32	-	-	100
Gentamycin	>8	-	-	100
Meropenem	64 to >64	-	-	100
Ertapenem	>2	-	-	100
TMP-SMX	>8/152	-	-	100
Tigecycline	≤0.25 to 1	75	-	25
Colistin	≤0.5 to 1	100	-	-
Aztreonam	2 to 32	-	25	75
Fosfomycin[a]	≤8 to 64	75	-	25
CLZ-TAZ	>64/4	-	-	100
CAZ-AVI	>32	-	-	100
MER-VAB	64 to >64	-	-	100
AZT-AVI	2 to 8	-	50	50

Abbreviations: AZT-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; CLZ-TAZ, ceftolozane-tazobactam; MER-VAB, meropenem-vaborbactam; PIP-TAZ, piperacillin-tazobactam; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]MIC for fosfomycin determined by agar dilution.

Data about treatment of BSI caused by NDM-producing *Enterobacterales* are very limited [8, 9]. Treatment regimens used in previous reports include colistin alone or in combination with aminoglycosides or meropenem, and the association of fosfomycin with meropenem [10–13]. In our series, all strains were in vitro resistant to ATM, while full susceptibility was restored when combination ATM + AVI was used. The efficacy of this combination relies on the activity that the monobactam ATM typically retains against MBLs but not against ESBLs (ie, all strains in our study produced CTX-M-15). In vitro studies demonstrated a synergistic effect of the combination of CAZ-AVI plus AZT against NDM-producing isolates [14, 15], and a clinical study including 5 patients with bacteremia caused by NDM-producing *Enterobacterales* showed that combination therapy with CAZ-AVI plus AZT is an effective therapeutic option [16]. Of interest, compared with other regimens, in our study surviving patients were more frequently treated with the combination of CAZ-AVI plus AZT. Although this finding was not statistically significant at Cox regression analysis, this is a potentially interesting finding that should be confirmed in larger, multicentric cohorts.

Table 2. NDM-Producing *Enterobacterales* BSI: Comparison Between Survivors and Nonsurvivors (Tuscany, Italy, 2018–2019)

	All Patients (n = 40)	Survivors (n = 23)	Nonsurvivors (n = 17)	*P*
Age, median (IQR), y	70.5 (55.25–77.75)	63 (48–76)	74 (67–82.5)	**.018**
Male sex	28 (70)	17 (73.9)	11 (64.7)	.530
Ward of hospitalization				
Medical wards	20 (50)	12 (52.2)	8 (47.1)	.687
ICU wards	13 (32.5)	8 (34.8)	5 (29.4)	
Surgery	7 (17.5)	3 (13)	4 (23.5)	
Comorbidities				
Cardiovascular disease	20 (50)	9 (39.1)	11 (64.7)	.110
Malignancy	19 (47.5)	9 (39.1)	10 (58.8)	.218
COPD	12 (30)	5 (21.7)	7 (41.2)	.185
Diabetes	12 (30)	8 (34.8)	4 (23.5)	.443
Chronic renal diseases	7 (17.5)	4 (17.4)	3 (17.6)	.983
Charlson comorbidity index, median (IQR)	4 (2–7)	3 (0–5)	6 (3–8.5)	**.010**
Immunosuppressive therapy,[a] previous 30 d	15 (37.5)	7 (30.4)	8 (47.1)	.283
Source of infection				
Unknown	10 (25)	3 (13)	7 (41.2)	.067
Urinary tract	10 (25)	7 (30.4)	3 (17.6)	
Intravascular device	9 (22.5)	8 (34.8)	1 (5.9)	
ABSSSI	6 (15)	3 (13)	3 (17.6)	
Respiratory tract	3 (7.5)	2 (8.7)	1 (5.9)	
Intra-abdominal	2 (5)	0	2 (11.8)	
NDM-producing strain rectal colonization	27 (67.5)	17 (89.5)	10 (62.5)	.058
Source control	20 (50)	12 (52.2)	8 (47.1)	.749
SOFA score, median (IQR)	4 (2–6)	4 (2–6)	5 (3–6.5)	.229
Length of hospital stay, median (IQR), d	23 (13–38)	26.5 (17.25–41.75)	19 (10–33)	.187
Septic shock	13 (32.5)	7 (30.4)	6 (35.3)	.746
Antibiotic regimens				
No in vitro active antibiotic therapy	14 (35)	5 (21.7)	9 (52.9)	.054
CAZ-AVI + ATM	12 (30)	10 (43.5)	2 (11.8)	
Colistin-based regimen[b]	9 (22.5)	4 (17.4)	5 (29.4)	
Others[c]	5 (12.5)	4 (17.4)	1 (5.9)	

Data are presented as No. (%), unless otherwise indicated. *P* values < .05 (indicating statistical significance) were reported in bold.

Abbreviations: ABSSSI, acute bacterial skin and skin structures infection; ATM, aztreonam; CAZ-AVI, ceftazidime-avibactam; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; ICU, intensive care unit; IQR, interquartile range.

[a]Including steroidal and nonsteroidal immunosuppressive therapy.

[b]Colistin was used in combination with meropenem (4 cases), fosfomycin (3 cases), tigecycline (1 case), AZT + piperacillin-tazobactam (1 case).

[c]Other therapies include: 1 patient treated with fosfomycin + tigecycline + amikacin (death); 1 patient treated with meropenem + tigecycline + fosfomycin; 1 patient treated with fosfomycin alone; 1 patient treated with tigecycline + meropenem; 1 patient treated with tigecycline alone.

We used CAZ-AVI at a dosage of 2.5 g every 8 hours and ATM at a dosage of 2 g every 8 hours in all cases (with dose adjustment according to renal function). Recently, therapeutic drug monitoring of CAZ-AVI and ATM performed in a child with BSI caused by KPC and NDM-producing *Enterobacter* spp. showed adequate serum concentrations of the combination CAZ-AVI plus ATM, both used at a dosage of 50 mg/kg every 8 hours [17]. If we translated this dosage in adult patients, the dose would have to be increased to 3–3.5 g every 8 hours for both ATM and CAZ-AVI. Overall, we observed a good clinical response of this combination therapy at standard dosages. Further pharmacokinetic studies are needed to assess the optimal dosage of ATM and CAZ-AVI in patients with BSI due to NDM-producing strains.

After the identification of the outbreak, several rapid actions were implemented to contain the spread of NDM-producing strains across health care facilities in the northwestern area of Tuscany. The measures included (i) mandatory screening by rapid molecular tests on admission and during hospitalization for all at-risk patients in medical wards and for all patients in the ICU, oncology, oncohematology, transplant unit, cardiac surgery, infectious diseases, acute rehabilitation; (ii) adoption of contact precautions in all cases; (iii) collection of data in a regional database and obligatory notification of all cases to a centralized laboratory; (iv) development of practical guidelines for the clinical management of NDM + cases; (v) dedicated medical and nursing staff and, in the tertiary hospital, identification of a dedicated ward for patients with colonization/infection by

NDM-producing *Enterobacterales*; (vi) educational meetings for all the professionals involved [18].

Our study has some limitations: (i) the number of BSIs is limited, but it is the largest cohort described in Europe; (ii) the multivariate analysis might be affected by the low number of cases; (iii) a high proportion of patients did not receive any active antibiotic therapy, which may have influenced the mortality rate. Nevertheless, this finding reflects clinical practice and the difficulties associated with early identification and appropriate treatment of infections caused by carbapenem-resistant *Enterobacterales* with multiple mechanisms of resistance.

In conclusion, the epidemiology of carbapenemase-producing *Enterobacterales* strains is changing over time, and new clones carrying new molecular mechanisms of resistance are emerging in some countries such as Italy. Bacteremia mediated by NDM-producing *Enterobacterales* is a highly lethal condition and requires prompt recognition and treatment. Although the combination of CAZ-AVI plus AZT appears to be a good therapeutic option in patients with NDM-producing bacteremia, the optimal regimen for the treatment of this infection is not defined and further studies are needed.

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References

1. European Centre for Disease Control and Prevention. Regional outbreak of New Delhi metallo-beta-lactamase-producing carbapenem-resistant Enterobacteriaceae, Italy, 2018–2019. June 2019. Available at: https://ecdc.europa.eu/sites/portal/files/documents/04-Jun-2019-RRA-Carbapenems%2C%20Enterobacteriaceae-Italy.pdf. Accessed 10 December 2019.
2. Falcone M, Russo A, Iacovelli A, et al. Predictors of outcome in ICU patients with septic shock caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae.* Clin Microbiol Infect **2016**; 22:444–50.
3. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA **2016**; 315:801–10.
4. Antonelli A, Arena F, Giani T, et al. Performance of the BD MAX™ instrument with Check-Direct CPE real-time PCR for the detection of carbapenemase genes from rectal swabs, in a setting with endemic dissemination of carbapenemase-producing Enterobacteriaceae. Diagn Microbiol Infect Dis **2016**; 86:30–4.
5. International Organization for Standardization, Clinical laboratory testing and in vitro diagnostic test systems. Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices—part 1: reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases. ISO 20776-1:2019. Available at: https://www.iso.org/standard/70464.html. Accessed on 18 January 2020.
6. Bankevich A, Nurk S, Antipov D, et al. SPAdes: a new genome assembly algorithm and its applications to single-cell sequencing. J Comput Biol **2012**; 19:455–77.
7. Falcone M, Paterson D. Spotlight on ceftazidime/avibactam: a new option for MDR gram-negative infections. J Antimicrob Chemother **2016**; 71:2713–22.
8. Snyder BM, Montague BT, Anandan S, et al. Risk factors and epidemiologic predictors of blood stream infections with New Delhi metallo-b-lactamase (NDM-1) producing Enterobacteriaceae. Epidemiol Infect **2019**; 147:e137.
9. Wu W, Feng Y, Tang G, et al. NDM metallo-beta-lactamases and their bacterial producers in health care settings. Clin Microbiol Rev. **2019**; 32:e00115-18.
10. Stone NR, Woodford N, Livermore DM, et al. Breakthrough bacteraemia due to tigecycline-resistant *Escherichia coli* with New Delhi metallo-β-lactamase (NDM)-1 successfully treated with colistin in a patient with calciphylaxis. J Antimicrob Chemother **2011**; 66:2677–8.
11. Avolio M, Vignaroli C, Crapis M, et al. Co-production of NDM-1 and OXA-232 by ST16 *Klebsiella pneumoniae*, Italy, 2016. Future Microbiol **2017**; 12:1119–22.
12. Petersen-Morfin S, Bocanegra-Ibarias P, Morfin-Otero R, et al. New Delhi metallo-beta-lactamase (NDM-1)-producing *Klebsiella pneumoniae* isolated from a burned patient. Am J Case Rep **2017**; 18:805–9.
13. Chien JM, Koh TH, Chan KS, et al. Successful treatment of NDM-1 *Klebsiella pneumoniae* bacteraemia in a neutropenic patient. Scand J Infect Dis **2012**; 44:312–4.
14. Marshall S, Hujer AM, Rojas LJ, et al. Can ceftazidime-avibactam and aztreonam overcome β-lactam resistance conferred by metallo-β-lactamases in Enterobacteriaceae? Antimicrob Agents Chemother. **2017**; 61:e02243–16.
15. Davido B, Fellous L, Lawrence C, et al. Ceftazidime-avibactam and aztreonam, an interesting strategy to overcome β-lactam resistance conferred by metallo-β-lactamases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. **2017**; 61:e01008–17.
16. Shaw E, Rombauts A, Tubau F, et al. Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing *Klebsiella pneumoniae* infection. J Antimicrob Chemother **2018**; 73:1104–6.
17. Yasmin M, Fouts DE, Jacobs M, et al. Monitoring ceftazidime-avibactam (CAZ-AVI) and aztreonam (ATM) concentrations in the treatment of a bloodstream infection caused by a multidrug-resistant *Enterobacter* sp. carrying both KPC-4 and NDM-1 carbapenemases. Clin Infect Dis. **In press**.
18. Bollettino Ufficiale della Regione Toscana. Indicazioni regionali per il contrasto alla diffusione di *Enterobacterales* produttori di metallo-beta lattamasi di tipo New-Delhi. Available at: https://www.regione.toscana.it/bancadati/BURT/Contenuto.xml?id=36299. Accessed 20 December 2019.

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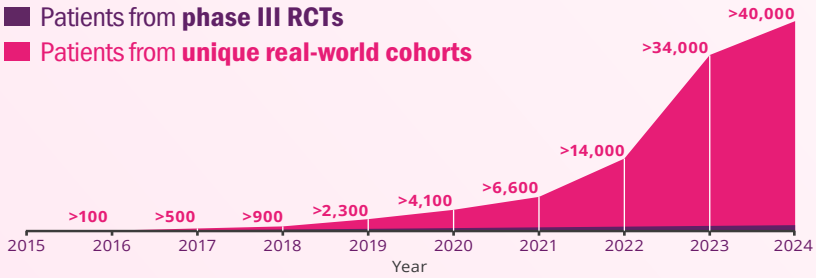

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DOVATO is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.[13]

Adverse events should be reported. Reporting forms and information can be found at **https://yellowcard.mhra.gov.uk/** or search for MHRA Yellowcard in the Google Play or Apple App store. Adverse events should also be reported to GSK on 0800 221441

REFERENCES

1. Maggiolo F et al. BMC Infect Dis 2022; 22(1): 782.
2. Taramasso L et al. AIDS Patient Care STDS 2021; 35(9): 342–353.
3. Ciccullo A et al. JAIDS 2021; 88(3): 234–237.
4. ViiV Healthcare. Data on File. REF-223795. 2024.
5. Cahn P et al. AIDS 2022; 36(1): 39–48.
6. Rolle C et al. Open Forum Infect Dis 2023; 10(3): ofad101.
7. Cordova E et al. Poster presented at 12th IAS Conference on HIV Science. 23–26 July 2023. Brisbane, Australia. TUPEB02.
8. De Wit S et al. Slides presented at HIV Glasgow. 23–26 October 2022. Virtual and Glasgow, UK. M041.
9. Llibre J et al. Clin Infect Dis 2023; 76(4): 720–729.
10. ViiV Healthcare. Data on File. REF-220949. 2024.
11. Rolle C et al. Poster presented IDWeek. 11–15 October 2023. Virtual and Boston, USA. 1603.
12. Slim J et al. Abstract presented IDWeek. 11–15 October 2023. Virtual and Boston, USA. 1593.
13. DOVATO. Summary of Product Characteristics. June 2023.

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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