Tenofovir alafenamide: An initial experience at Groote Schuur Hospital, Cape Town, South Africa

A Geragotellis,[1] BMedSci Hons, 4th-year medical student; **S Patel,**[1] 3rd-year medical student; **M Sonderup,**[2] MB ChB, MMed (Med); **N Wearne,**[3] BA Med Sci, MB ChB; **Z Barday,**[3] MB ChB; **L Sanglay,**[4] BPharm; **V Naicker,**[4] BPharm; **C W Spearman,**[2] MB ChB, PhD

[1] *Faculty of Health Sciences, University of Cape Town, South Africa*
[2] *Division of Hepatology and Department of Medicine, Faculty of Health Sciences, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa*
[3] *Division of Nephrology and Hypertension, Department of Medicine, Faculty of Health Sciences, University of Cape Town Groote Schuur Hospital, Cape Town, South Africa*
[4] *Pharmacy Services, Groote Schuur Hospital, Cape Town, South Africa*

Corresponding author: *M Sonderup (mark.sonderup@uct.ac.za)*

Background. Hepatitis B virus (HBV) remains endemic in South Africa (SA), with a concomitantly high prevalence of HIV co-infection. Chronic kidney disease in these subpopulations also has a high prevalence. Tenofovir is an important component of management, but the associated risk of nephrotoxicity makes dosing a challenge in patients with impaired kidney function. A new formulation, tenofovir alafenamide fumarate (TAF), with a more favourable renal toxicity profile, is now available.
Objectives. To evaluate our initial experience of TAF use at Groote Schuur Hospital, Cape Town.
Methods. We retrospectively reviewed patients with HBV mono-infection and HIV-HBV co-infection who were initiated on TAF since 2018. We recorded all relevant demographic, serological, virological and biochemical data from patient records. Adherence was documented by pill collection at the pharmacy.
Results. A total of 26 patients were included in the evaluation, median (interquartile range (IQR)) age 48 (39 - 51) years, 73% (n=19) male, 27% (n=7) hepatitis B e-antigen-positive, and 46% (n=12) HIV co-infected. The median (IQR) duration of treatment with TAF was 13 (9 - 15) months. The median (IQR) baseline creatinine level was 180 (130 - 227) µmol/L, with significant improvement at 12 months, 122 (94 - 143) µmol/L; p=0.017. Reflecting this change, the estimated glomerular filtration rate improved significantly from baseline to month 12 (42 (25 - 52) and 51 (48 - 68) mL/min/1.73 m^2, respectively; p=0.023). Similarly, serum alanine aminotransferase (ALT) normalised from a baseline of 33 (18 - 52) to 18 (15 - 24) U/L at month 12 (p=0.012). HBV DNA viral load also declined, from a baseline of $\log_{10}$ 4.04 (2.5 - 7.8) IU/mL to a median of $<\log_{10}$ 1.3 IU/mL at month 12. HIV viral load was less than the lower level of quantification at months 6 and 12.
Conclusions. TAF was well tolerated, with stable and significantly improving kidney function throughout a 12-month follow-up period. Serum ALT normalised, mirrored by declining HBV viral load. HIV viral load remained undetectable at 6 and 12 months.

S Afr Med J 2022;112(2):113-116. https://doi.org/10.7196/SAMJ.2022.v112i2.16188

Hepatitis B virus (HBV) remains endemic in South Africa (SA).[1] Hepatitis B surface antigen (HBsAg) seroprevalence ranges from 0.5% to 8%, with HBV co-infection observed in 0.4 - 9.4% of those who are HIV infected.[2-4] Chronic HBV infection elevates the risk of cirrhosis, decompensation and hepatocellular carcinoma (HCC), even in the absence of cirrhosis.[5] Significant therapeutic advances have been made over the past two decades. While a functional cure for HBV, characterised by the loss of HBsAg, is currently a targeted goal, most HBV-infected individuals require a lifelong suppressive nucleos(t)ide analogue treatment regimen. Clinical outcomes with long-term therapy are very good, leading to a significant reduction in the development of chronic liver disease, stabilisation and even regression of fibrosis, and a reduction in HCC risk.[6]

Several drugs have been approved for HBV treatment over the past 20 years, including lamivudine, entecavir and tenofovir. Tenofovir, constituted as tenofovir disoproxil fumarate (TDF) in a 300 mg tablet, is a first-line nucleos(t)ide analogue used to manage chronic HBV.[7] It is also active against HIV as a nucleoside reverse transcriptase inhibitor and is a major constituent of combination antiretroviral therapy (ART) regimens.[8] The therapeutic value of TDF is offset by its risk of bone and kidney toxicity. Chronic kidney disease (CKD) is associated with both chronic HBV and HIV infection.[9] CKD prevalence in HIV has been reported at 6.4% in a meta-analysis, depending on the methods used to assess renal function.[10] In HIV mono-infected patients, an ART regimen can be adjusted for reductions in creatinine clearance. Lamivudine dosing can be renally adjusted and abacavir substituted for TDF. However, in patients with HBV mono-infection or HIV co-infection, options are limited. Lamivudine resistance can develop, quite rapidly in those with co-infection, with HBV virological breakthrough, rising viral loads and risk of HBV flares and decompensation. For those failing lamivudine, TDF prescription is necessary as it is the only nucleoside reverse transcriptase inhibitor fully active against lamivudine resistance. In patients who are HIV-HBV co-infected, ART must include two drugs active against HBV, so TDF is combined with either lamivudine or emtricitabine. First-line treatment for HBV mono-infection is either TDF or entecavir. Management options are therefore limited in patients with established CKD or those who develop kidney injury on TDF-based therapy. Entecavir is an alternative first-line option that may be dose-adjusted to kidney

function, but its cost is prohibitive, as no generics are currently available in SA.

Tenofovir alafenamide fumarate (TAF) is a US Food and Drug Administration-approved prodrug of TDF that is well tolerated and equally efficacious, with superior plasma stability.[11] As such, the delivery of the active metabolite, tenofovir diphosphate, to hepatocytes is significantly more efficient, which facilitates a lower daily dose (25 mg) of TAF necessary to achieve a therapeutic concentration. Crucially, the reduction in systemic exposure circumvents the potential kidney and bone toxicities observed with TDF 300 mg daily dosing.[12] TAF is registered for use in patients with a glomerular filtration rate ≥15 mL/min. Global HBV guidance now recommends TAF over TDF in chronic HBV patients with or at risk of kidney or bone disease.[13,14] TAF (Vemlidy; Gilead Sciences) has now been approved by the South African Health Products Regulatory Authority (SAHPRA), but has not as yet been marketed.[15] To date it remains unavailable, but generic TAF, as an interim measure, has been obtained from India via a SAHPRA section 21 process.

Objectives

Local data assessing TAF in patients with established CKD are not yet available. With the limited availability of TAF, we elected to review our initial experience with its use.

Methods

Generic TAF (Tafnat; Natco Pharma, India), available at Groote Schuur Hospital (GSH) in Cape Town since 2018 via a SAHPRA section 21 certificate process, was used at a dose of 25 mg/d as a substitute for TDF in HBV mono-infected or HBV-HIV co-infected patients with impaired kidney function. Criteria for use were patients with kidney impairment (estimated glomerular filtration rate (eGFR) <50 mL/min), ineligible for either commencing or resuming TDF, or those with kidney impairment failing lamivudine for their HBV management either alone or as part of ART. For HBV mono-infected patients, TAF was used as monotherapy or added to lamivudine. For those who were HIV-HBV co-infected, TAF was added to kidney function-adjusted lamivudine plus either a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor or dolutegravir as per standard ART guidelines in SA.

We retrospectively reviewed the records of patients who initiated TAF. Demographic, biochemical, serological and virological (hepatitis B e antigen (HBeAg) and HBV viral load (Xpert HBV Viral Load; Cepheid)) data were captured at baseline and at 3, 6 and 12 months, where available, after initiating TAF. The lower level of quantification (LLoQ) of the HBV DNA platform, the Cobas Amplicor platform (Roche AG, Switzerland), is <20 IU/mL. To maintain uniformity, the eGFR was recorded for all participants using the laboratory-generated eGFR of the Modification of Diet in Renal Disease equation. Pill collection records from the GSH pharmacy were also used to qualify patients for analysis based on their adherence to therapy, and similarly to exclude non-adherent patients from the analysis. Ethics approval was granted by the University of Cape Town Human Research Ethics Committee (ref. no. HREC 141/2021).

Statistical analysis

For continuous variables, all values are expressed as means with standard deviations or medians and interquartile ranges (IQRs) for parametric and non-parametric data, respectively. Baseline and on-treatment data are summarised using standard descriptive characteristics. Where appropriate, differences between qualitative parameters were evaluated using the Wilcoxon rank-sum test. Statistical analysis was performed using Medcalc v19.5.3 (MedCalc Software, Belgium).

Results

The baseline characteristics of 26 patients (median age 48 years) who were included in the audit are detailed in Table 1. Most (73%; *n*=19) were male. Almost one-third (27%) were HBeAg-positive. Just under half (46%; *n*=12) were HIV co-infected, with a pre-TAF median CD4 count of 286 cells/μL. Of the 12 HIV co-infected patients, 7 (58%) were switched to TAF from their existing ART regimens with HIV viral loads less than the level of detection at the time of switching. Seventy-three percent (*n*=19) were concomitantly also on lamivudine – 53% (*n*=10/19) were HIV co-infected, and the other 47% (*n*=9/19) were HBV mono-infected and had failed lamivudine monotherapy for chronic HBV treatment. The median duration of treatment with TAF of the cohort was 13 months.

Table 2 shows that the median (IQR) baseline creatinine level was 180 (130 - 227) μmol/L when patients initiated or were switched to TAF. At 12 months' follow-up, creatinine significantly improved on TAF (p=0.017). Similarly, eGFR improved significantly in the first 12 months of follow-up (p=0.023). Serum ALT (p=0.012) and aspartate aminotransferase (p=0.002) levels improved significantly on TAF. These changes were paralleled by a decline in HBV DNA viral load, with the median HBV viral load at 6 and 12 months declining to low levels (Table 3). At 6 months, 58% of patients had HBV viral loads less than the LLoQ; at 12 months 72% were below the LLoQ (Fig. 1). The median (IQR) HBV viral load of those with detectable HBV DNA and greater than the LLoQ at 6 and 12 months was 1 088 (270 - 1 × 10^4) IU/mL and 126 (49 - 1 027) IU/mL, respectively. All HIV viral loads were below the LLoQ at 6 and 12 months (data not shown).

In retrospectively reviewing patient records, beyond 12 months of follow-up, 3 deaths were noted – 2 patients with HIV-HBV co-infection (one death due to advanced HIV and mycobacterial infection and sepsis complicated by acute-on-chronic kidney disease, and the second from high-grade B-cell lymphoma), and 1 patient with HBV cirrhosis complicated by hepatopulmonary syndrome. A single patient was noted to undergo HBsAg seroclearance at 24 months after initiating TAF.

Discussion

We present the first data from SA of our experience with a small cohort of patients managed with TAF as part of their hepatitis B or HBV/HIV co-infection treatment regimen. These patients all

Table 1. Baseline characteristics of patients included in the study (*N*=26)

Age (years)	
Mean (SD)	47.7 (12.6)
Median (IQR)	48 (39 - 51)
Male, *n* (%)	19 (73)
HBeAg-positive, *n* (%)	7 (27)
HIV co-infected, *n* (%)	12 (46)
CD4 at baseline (cells/μL)	
Mean (SD)	332 (182)
Median (IQR)	286 (181 - 587)
Duration of treatment with TAF (months), median (IQR)	13 (9 - 15)

SD = standard devation; IQR = interquartile range; HBeAg = hepatitis B e antigen; TAF = tenofovir alafenamide fumarate.

Table 2. Laboratory characteristics over the duration of follow-up

Laboratory characteristic	Baseline (*N*=26)	Month 3	Month 6	Month 12	*p*-value
Creatinine (μmol/L), median (IQR)	180 (130 - 227)	132 (107 - 153)	124 (96 - 144)	122 (94 - 143)	0.017
eGFR (ml/min/1.73 m^2), median (IQR)	42 (25 - 52)	47 (30 - 51)	49 (35 - 54)	51 (48 - 68)	0.023
ALT (U/L), median (IQR)	33 (18 - 52)	24 (19 - 36)	19 (14 - 25)	18 (15 - 24)	0.012
AST (U/L), median (IQR)	38 (27 - 55)	25 (20 - 42)	25 (20 - 31)	23 (19 - 28)	0.002
TBil (μmol/L), median (IQR)	9 (5 - 15)	8 (5 - 10)	9 (4 - 11)	8 (5 - 12)	0.75

IQR = interquartile range; eGFR = estimated glomerular filtration rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBil = total bilirubin.

Table 3. Hepatitis B virological changes over the duration of follow-up

	Baseline (*N*=26)	Month 6	Month 12
Hepatitis B viral load (IU/mL), median (IQR)	1.35×10^4 (517 - 6.23×107)	<20 (20 - 270)	<20 (<20 - 53)
HBV DNA viral load (log_{10} IU/mL), median (IQR)	4.04 (2.5 - 7.8)	1.3 (<1.3 - 1.7)	<1.3

IQR = interquartile range; HBV = hepatitis B virus.

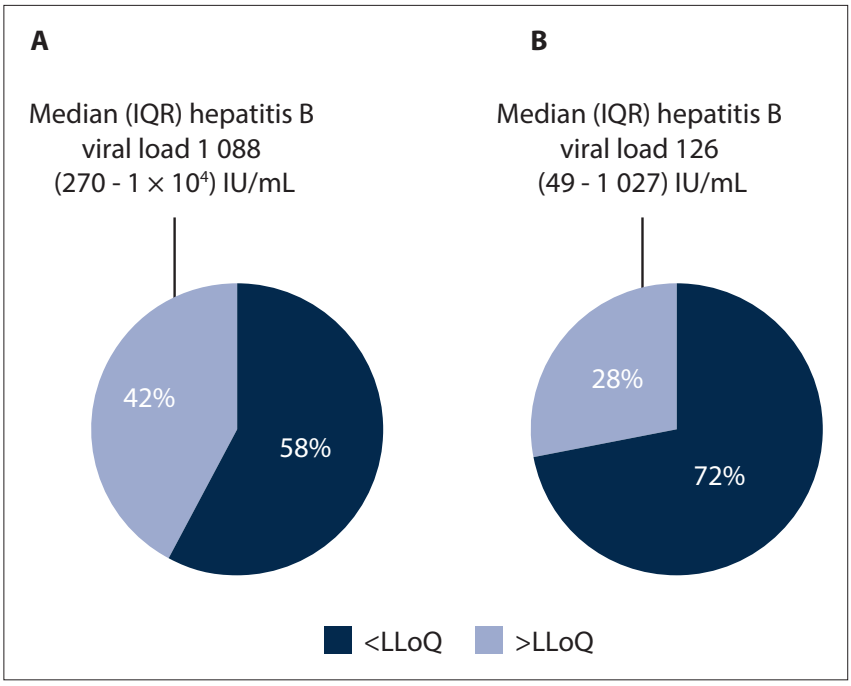

Fig. 1. Hepatitis B viral loads <LLoQ at 6 months (A) and 12 months (B). (LLoQ = lower limit of quantification; IQR = interquartile range.)

had impaired kidney function, mandating their consideration for a non-TDF-based regimen. HIV-positive patients are at risk of TDF-related kidney toxicity in addition to HIV-associated and non-HIV-associated kidney comorbidity.[16,17] TDF renal toxicity is not infrequently encountered in SA.[18] Guidelines for TDF dosing in renal impairment do exist and are based on creatinine clearance.[19] However, owing to resource constraints, we face the challenge that patients with CKD may not necessarily access kidney replacement therapy should their kidney disease progress. Equally, long-term lamivudine monotherapy is not ideal in HBV mono-infection and is not advised in HIV-HBV co-infection.

The development of TAF has been progressive, allowing for a therapeutic option that avoids the potential kidney toxicity risk. We have demonstrated that kidney function in our cohort did not progress or worsen – on the contrary, it improved significantly. This finding is encouraging and may reflect patients who were on TDF with potential nephrotoxicity but switched to TAF with a consequent improvement in kidney function. It suggests that patients tolerate TAF well despite initiating therapy at a baseline of advanced CKD.

Unsurprisingly, HBV viral loads declined on treatment, with most patients below the LLoQ at 6 and 12 months. The slower rate of HBV viral load decline in patients on tenofovir is well recognised. Given the high barrier to resistance of tenofovir, this fortunately does not influence the potential for the development of resistance.[20] Serum ALT, as a surrogate of liver necro-inflammation, significantly improved on TAF. Equally, this mirrored the decline in HBV viral load. A feature noted with TAF in previous studies is the more rapid normalisation of serum ALT compared with TDF.[21] Although we were not comparing our cohort with TDF, we observed significant serum ALT normalisation over the 12-month follow-up period. We did not observe any loss of HBsAg, reported in ~1% of patients on TAF.[22]

Study limitations

Our study had limitations. It was a retrospective review on a small sample size, and the only TAF discontinuations occurred in 3 patients beyond 12 months who died. We also did not assess bone health in terms of bone mineral density; our median 13-month follow-up period in this cohort would have been too short to provide thorough evaluation compared with larger, multicentre TAF trials that have employed 12-month endpoints.[23,24] In addition, given the extent of CKD in our patients, renal osteodystrophy may have made the benefits of TAF difficult to assess given existing poor baseline bone health.

Conclusions

TAF provides an advancement in the management of hepatitis B and HIV, with or without co-infection, notably in patients with chronic kidney disease. In our initial experience, albeit in a small cohort of patients, we have demonstrated stabilisation and improvement in kidney function in those on TAF. Similarly, hepatitis B and HIV therapeutic response was excellent.

TAF represents a significant therapeutic advance in a subgroup of patients who are difficult to manage.

Declaration. None.

Acknowledgements. We thank the Drug and Therapeutics Committee for supporting our acquisition of TAF for patients eligible for the therapy.

Author contributions. MS conceived the study. AG and SP gathered all the relevant data and drafted the manuscript together with MS. All authors contributed to the further development and editing of the final manuscript.

Funding. None.

Conflicts of interest. None.

1. Kew MC. Hepatitis B virus infection: The burden of disease in South Africa. South Afr J Epidemiol Infect 2008;23(1):4-8. https://doi.org/10.1080/10158782.2008.11441293
2. Firnhaber C, Reyneke A, Schulze D, et al. The prevalence of hepatitis B co-infection in a South African urban government HIV clinic. S Afr Med J 2008;98(7):541-544.
3. Samsunder N, Ngcapu S, Lewis L, et al. Seroprevalence of hepatitis B virus: Findings from a population-based household survey in KwaZulu-Natal, South Africa. Int J Infect Dis 2019;85:150-157. https://doi.org/10.1016/j.ijid.2019.06.005
4. Prabdial-Sing N, Makhathini L, Smit SB, et al. Hepatitis B sero-prevalence in children under 15 years of age in South Africa using residual samples from community-based febrile rash surveillance. PLoS ONE 2019;14(5):e0217415. https://doi.org/10.1371/journal.pone.0217415
5. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009;49(5 Suppl):S45-S55. https://doi.org/10.1002/hep.22898
6. Suk-Fong Lok A. Hepatitis B treatment: What we know now and what remains to be researched. Hepatol Commun 2019;3(1):8-19. https://doi.org/10.1002/hep4.1281
7. Marcellin P, Wong D, Sievert W, et al. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. Liver Int 2019;39(10):1868-1875. https://doi.org/10.1111/liv.14155
8. Nelson MR, Katlama C, Montaner JS, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: The first 4 years. AIDS 2007;21(10):1273-1281. https://doi.org/10.1097/qad.0b013e3280b07b33
9. Du Y, Zhang S, Hu M, et al. Association between hepatitis B virus infection and chronic kidney disease: A cross-sectional study from 3 million population aged 20 to 49 years in rural China. Medicine (Baltimore) 2019;98(5):e14262. https://doi.org/10.1097/md.0000000000014262
10. Ekrikpo UE, Kengne AP, Bello AK, et al. Chronic kidney disease in the global adult HIV-infected population: A systematic review and meta-analysis. PLoS ONE 2018;13(4):e0195443. https://doi.org/10.1371/journal.pone.0195443
11. Lampertico P, Buti M, Fung S, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: A randomised, double-blind, phase 3, multicentre non-inferiority study. Lancet Gastroenterol Hepatol 2020;5(5):441-453. https://doi.org/10.1016/s2468-1253(19)30421-2
12. Lee BT, Chang M, Lim C, Bae HS, Fong TL. Bone and renal safety profile at 72 weeks after switching to tenofovir alafenamide in chronic hepatitis B patients. JGH Open 2021;5(2):258-263. https://doi.org/10.1002/jgh3.12481
13. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67(4):1560-1599. https://doi.org/10.1002/hep.29800
14. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370-398. https://doi.org/10.1016/j.jhep.2017.03.021
15. South African Health Products Regulatory Authority (SAHPRA). Vemlidy 25 mg film-coated tablets. October 2020. https://www.sahpra.org.za/wp-content/uploads/2021/02/Vemlidy_PI_Gilead-Sciences-South-Africa-Pty-Ltd_Old-MCC-format23-October-2020.pdf (accessed 1 November 2021).
16. Mocroft A, Lundgren JD, Ross M, et al. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: A prospective international cohort study. Lancet HIV 2016;3(1):e23-e32. https://doi.org/10.1016/s2352-3018(15)00211-8
17. Wever K, van Agtmael MA, Carr A. Incomplete reversibility of tenofovir-related renal toxicity in HIV-infected men. J Acquir Immune Defic Syndr 2010;55(1):78-81. https://doi.org/10.1097/qai.0b013e3181d05579
18. Brennan A, Evans D, Maskew M, et al. Relationship between renal dysfunction, nephrotoxicity and death among HIV adults on tenofovir. AIDS 2011;25(13):1603-1609. https://doi.org/10.1097/qad.0b013e32834957da
19. Swanepoel CR, Atta MG, D'Agati VD, et al. Kidney disease in the setting of HIV infection: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2018;93(3):545-559. https://doi.org/10.1016/j.kint.2017.11.007
20. Pan CQ, Chang TT, Bae SH, et al. Antiviral kinetics of tenofovir alafenamide and tenofovir disoproxil fumarate over 24 weeks in women of childbearing potential with chronic HBV. PLoS ONE 2021;16(5):e0251552. https://doi.org/10.1371/journal.pone.0251552
21. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 2018;68(4):672-681. https://doi.org/10.1016/j.jhep.2017.11.039
22. Byrne R, Carey I, Agarwal K. Tenofovir alafenamide in the treatment of chronic hepatitis B virus infection: Rationale and clinical trial evidence. Therap Adv Gastroenterol 2018;11:1756284818786108. https://doi.org/10.1177/1756284818786108
23. Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: A randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet Infect Dis 2016;16(1):43-52. https://doi.org/10.1016/s1473-3099(15)00348-5
24. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: Two randomised, double-blind, phase 3, non-inferiority trials. Lancet 2015;385(9987):2606-2615. https://doi.org/10.1016/s0140-6736(15)60616-x

Accepted 12 November 2021.