

Delamanid expanded access novel treatment of drug resistant tuberculosis [Corrigendum]

Rustomjee R, Zumla A. Delamanid expanded access novel treatment of drug resistant tuberculosis. *Infection and Drug Resistance*. 2015;8:359–366.

Dr Rustomjee and Professor Zumla are grateful to a reader for raising some issues regarding referencing, and interpretation of their paper, and would like to clarify and address these issues.

- Page 1, first paragraph, “While this drug has been included in international guidance for the treatment of MDR-TB since April 2014,⁶ [...]”. The reader queried the statement, as the publishing date of the reference is October 2014. The authors respond: The referenced WHO guideline was published in October 2014; reporting on the meeting held April 14–15, 2014.

- Page 1, first paragraph “By end of December 2014, less than ten patients outside clinical settings had received delamanid”. The reader queried the citation of reference 5 here, and asked for a statement regarding the number of patients.

The authors respond: We have not been able to find the number of individuals who received Delamanid outside of clinical trials by the end of December 2014, Nevertheless, a year later (December 2015) just over 100 patients received Delamanid outside of clinical trial settings. (See Furin et al. In reply. QTc prolongation and delamanid: access and safety. *Int J Tuberc Lung Dis*. 2015, 19(10):1262–1263.

- Page 2, second paragraph, “Whilst this long awaited donation is aimed at delivering, at least, in part, on the “20 by 2020” goal, which is to ensure delamanid reaches 20% of all MDR-TB diagnosed and treated patients by 2020⁸; to date limited information can be obtained as to the timeframe and mechanism for this expansion of access.^{7,8}” The reader queries the placement of citations, implying a link to the two projects.

The authors respond: The sentence is incorrectly referenced, and should appear as: “Whilst this long awaited donation; 7 together with a UNITAID funded project

known as “The endTB project” 8 is aimed at delivering, at least, in part, on the “20 by 2020” goal, which is to ensure delamanid reaches 20% of all MDR-TB diagnosed and treated patients by 2020; to date limited information can be obtained as to the timeframe and mechanism for this expansion of access.”

The reader also advises that the FighTBack Initiative announced by Otsuka in April 2015 is not a donation program, but rather a comprehensive access strategy.

The authors respond: The announcement (reference 7) makes reference to a “targeted access donation programme”.

- Page 1, first paragraph, “Further, there are significant exclusions to the countries listed in the donation announcement, eg, South Africa, with amongst the highest burden of MDR TB and amongst the largest patient contributors to the trials that produced the evidence for the safety and efficacy of delamanid, is precluded from the donation”⁷, the reader queries this, as no countries are listed in the reference.

The authors respond: We acknowledge this and suggest the revised text “Further, it is expected that nearly half of the high TB burden countries may not be recipients. Participation in the endTB project covers 17 countries as indicated by MSF/PIH. The company has indicated that additional discussions are taking place for access in South Africa and other countries via the Stop TB Partnership’s Global Drug Facility.”

- Page 2, second paragraph, “It is ethically imperative that delamanid becomes available in countries where clinical trials have been performed.⁹ Thus far, only a few of those in dire need (<100 patients), have successfully accessed this drug through either compassionate use or post-trial obligations of the trial sponsors to patients and their communities.”⁹ The reader queries the citation of reference 9 here. The authors respond: This is our opinion and thus no reference is required.

- Page 4, first paragraph under heading “Safety”, “QT prolongation, the most troubling side effect of delamanid,

is also caused by other MDR-TB drugs like bedaquiline, clofazimine, and moxifloxacin. No studies have been done yet to show whether the effects of these drugs on heart rhythm are additive, or if the drugs are safe to use together.” The reader notes that a 2015 publication regarding Phase II trial of delamanid includes a subset of patients treated with moxifloxacin.

The authors respond: This information was not available when we wrote the article.

- Page 4, first paragraph under heading “Safety”, “A National Institutes of Health AIDS Clinical Trials Group study (A5343) will investigate drug–drug interactions and combined QT effects of co-administered bedaquiline and delamanid, with results expected in 2016.³¹” The reader queries the use of reference 31 here, as it does not mention a completion date, but that it is expected in April 2017. The authors respond: Prior to delay of the trial, early results were expected 2016. Reference 31 could now be changed to: National Institute of Allergy and Infectious Diseases (NIAID). Evaluating the safety, tolerability, and pharmacokinetics of bedaquiline and delamanid, alone and in combination for drug-resistant pulmonary tuberculosis. Available from <https://clinicaltrials.gov/ct2/show/NCT02583048>. NLM identifier NCT 02583048.
- Page 5, second paragraph, “Delamanid and its metabolites have also been shown to be excreted into breast milk.¹³” The reader queries this statement in relation to reference 13. The authors respond: The reference citation is incorrect, and the sentence should read “Delamanid and its metabolites have also been shown to be excreted into breast milk of rats.^{15,29}”
- Page 6, first paragraph under the heading “Global access”, “Thus far Deltyba has been launched only in the United Kingdom and Germany despite marketing authorization for the whole of Europe”. The reader believes there is no evidence to support this statement, and that Deltyba has been accessed by patients in over 10 countries in the European Union. The authors respond: The text should be replaced with, “Deltyba has been accessed by patients in over 10 countries in the European Union”.
- Page 6, first paragraph under the heading “Global access”, “The cost of a 6-month treatment course in these countries is prohibitive at over US\$33,000 for a 6-month course of 100 mg twice daily.⁹” The reader queries the use of reference 9, as it does not mention delamanid, or its price. The authors respond: The correct citation here is Diel et al for the Deltyba price in Europe which is €37.5 per tablet or US\$41.98. <http://dx.doi.org/10.1016/j.rmed.2015.01.017> by extrapolation; for a 6 month course of 100 mg twice daily the cost could exceed US\$25,000.
- Page 6, first paragraph under the heading “Global access”, “High TB burden countries in Eastern Europe such as Estonia, Latvia, Lithuania, and Romania, as yet have not had access to the drug outside of enrollment in the clinical trials – specific plans to broaden the access to this drug have not been made public neither are labeling and educational materials available for most countries, which may further delay access where there is an urgent need for access to MDR-TB treatment options.” The reader advises that this references does not support the statement, which is incorrect regardless. The authors respond: We rephrase as follows: “High TB burden countries in Eastern Europe such as Lithuania, and Romania have not yet incorporated delamanid into their national TB control programs despite approval in European Union since April 2014. Nor has specific plans to broaden the access to this drug; or provide specific labeling or educational material been made public, yet.”
- Page 6, second paragraph under the heading “Global access”, “Further, to date, despite an intention to widen access to delamanid outside the European Union and Japan, high TB burden countries or where clinical trials were conducted such as People’s Republic of China, Philippines, Egypt, Korea, Moldova, Peru, and South Africa have not been engaged in terms of developing a licensing strategy.⁹ Nor has expanded access under compassionate use been overwhelmingly enthusiastic.” The reader feels that the reference is not correct, nor is the information supplied correct. The authors respond: Reference 9 is incorrect. We rephrase as: “Further, to date, despite an intention to widen access to delamanid outside the European Union, Korea and Japan where regulatory approval has been achieved; high TB burden countries; or where clinical trials were conducted such as People’s Republic of China, Philippines, Egypt, Moldova, Peru, and South Africa have not been engaged in terms of developing a licensing strategy although regulatory submissions may be eminent or pending.”

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