the possibility that the role of dolutegravir in second-line therapy becomes less relevant. Indeed, WHO recommends a protease inhibitor (with NRTIs) as second-line treatment after failure of a dolutegravir-based first-line regimen.[3] There is the additional limitation that dolutegravir is not yet considered safe for young children and women of childbearing age without access to contraception, which are a majority of patients in many LMICs.

Better efficacy and tolerability of second-line ART can greatly improve the prognosis of HIV-infected populations in LMICs. Nonetheless, there is an urgent need for routine ART programmes to monitor emerging dolutegravir resistance and to quantify its clinical effects and potential for transmission.

Raph L Hamers
Eijkman-Oxford Clinical Research Unit, Eijkman Institute for Molecular Biology, and Faculty of Medicine Universitas Indonesia, Jakarta 10430, Indonesia; Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK; and Amsterdam Institute for Global Health and Development, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands
raph.hamers@ndm.ox.ac.uk

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Clostridium difficile infection trials: what is the primary endpoint?

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Over the past 10 years, *Clostridium difficile* has emerged as a major enteric pathogen in Europe and the USA. In 2009, a surveillance study identified 336 600 hospital admissions involving *C difficile* in the USA, representing 0·9% of all hospital stays.[1] Another study showed that *C difficile* was responsible for almost half a million infections and associated with 29 000 deaths in 2011 in the USA.[1] The challenge with *C difficile* infection is not only to cure the patient but also to prevent recurrences. The risk of recurrence more than doubles after two or three recurrences,[2] emphasising the role of adequate initial treatment.

Before 2012, the treatment of *C difficile* infection relied on two molecules, metronidazole and vancomycin, but since then several new drugs have become available or are being studied. The efficacy of these new treatments need to be evaluated on the basis of clinical cure of the episode and prevention of recurrence, represented by sustained clinical cure. Fidaxomicin was the first new drug to be included in European and American guidelines.[3,4] The two pivotal trials of fidaxomicin showed that it provided a significantly lower number of recurrences and superior sustained clinical cure.[5,6]

In *The Lancet Infectious Diseases*, Dale Gerding and colleagues[7] report the results of two double-blind, placebo-controlled, non-inferiority, randomised controlled phase 3 trials (IMPACT 1 and 2) evaluating a

new molecule, cadazolid, compared with vancomycin. Cadazolid is a novel quinoxolidinone with a potent in-vitro bactericidal activity against *C difficile*. The primary outcome of these trials was clinical cure, defined as resolution of diarrhoea on treatment and maintained for 2 days; sustained clinical cure and recurrence were assessed as secondary endpoints. Non-inferiority of cadazolid compared with vancomycin was shown in one of the two trials (IMPACT 1; treatment difference –1·4 [95% CI –7·2 to 4·3] for modified intention to treat and –4·1 [–9·2 to 1·0] for per protocol); superiority of sustained clinical cure was not shown in either. Populations were similar in IMPACT 1 and 2 and in the fidaxomicin trials, with the proportion of patients enrolled for a first recurrence ranging from 18·6% to 20·8% in IMPACT 1 and 2, compared with 17·1% to 14·9% in the fidaxomicin trials.[5,8] In the cadazolid study, about 18% of *C difficile* infections were severe, also similar to the fidaxomicin trials. The proportion of patients cured by vancomycin was also similar in the trials.

The results of the IMPACT studies are disappointing, and the future of cadazolid is unclear. One potential argument to support the use of cadazolid versus vancomycin would have been a benefit on gut microbiota dysbiosis, but the authors suggest only a marginal difference between the two drugs, although we don't have the data. However, these studies raise an important concern in all studies done for *C difficile* infection: the heterogeneity in definitions. What is clinical cure? How do we define severity? What is the final endpoint to define sustained clinical cure? In these studies,[7] Gerding and colleagues assessed an "investigators' assessment" of clinical cure in exploratory analyses. Cadazolid was non-inferior to vancomycin when this approach was used. This finding will not dramatically change the drug's profile as it does not change the effect on recurrence, but, as the authors discuss, many differences exist between trials in their design and endpoints. The definition of severity also differs between international guidelines[3,4] and trials.[5,6,9,10] In *C difficile* infection, sustained clinical cure is analysed 30–90 days after the end of treatment.[5,6,11,12] Considering that recurrence can occur after 30 days, a 30-day window for assessing sustained clinical cure might overestimate efficacy. 8% of recurrences occurred in this period in the control group in a trial of bezlotoxumab,[13] and 2% in patients treated with vancomycin in the EXTEND trial.[11] IMPACT 1 and 2 do not provide a strong basis for the implementation of cadazolid in treatment of *C difficile* infection, but they do underline the need for strong and uniform definitions and the development of new tools to assess the response to treatment.

Benoit Guery
Infectious Diseases Service, Department of Medicine, University Hospital and University of Lausanne, Lausanne, Switzerland
benoit.guery@chuv.ch

I have participated in the boards of MSD, Pfizer, and Astellas.

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