Dolutegravir for second-line antiretroviral therapy

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See Articles page 253

As the global cohort of people with HIV-1 who receive life-saving antiretroviral therapy (ART) has expanded and matured, the numbers of patients with virological failure on a first-line regimen of a non-nucleoside reverse transcriptase inhibitor (NNRTI) with two nucleoside reverse transcriptase inhibitors (NRTIs) needing a switch to second-line therapy will inevitably rise.[1,2] Until December 2018, WHO recommended a ritonavir-boosted protease inhibitor (with two NRTIs) as second-line treatment, but these drugs are associated with dyslipidaemia, gastrointestinal side-effects, and bone, renal, and cardiovascular toxicities.[3]

In *The Lancet Infectious Diseases*, the DAWNING trial by Michael Aboud and colleagues[4] assesses much-needed alternative second-line therapy without a protease inhibitor as the core drug. Combined with two NRTIs, of which at least one was fully active according to resistance genotyping at study screening, the integrase strand transfer inhibitor dolutegravir was superior to the protease inhibitor lopinavir plus ritonavir, in terms of the proportion of patients achieving viral suppression at week 48, defined as plasma HIV-1 RNA less than 50 copies per mL (261 [84%] of 312 in the dolutegravir group *vs* 219 [70%] of 312 in the lopinavir plus ritonavir group), as well as adverse events and patient satisfaction.[4] The study findings have led WHO to recommend dolutegravir plus two optimised NRTIs as a preferred second-line regimen for patients whose non-dolutegravir-based first-line regimen is no longer effective.[3]

In subgroup analyses, a greater proportion of participants who had NRTI resistance at study screening achieved viral suppression (in either group) than those receiving two fully active NRTIs,[4] which extends previous findings in protease inhibitor-based second-line regimens.[5,6] This result suggests that patients with first-line NRTI resistance might have better adherence (and therefore greater drug selective pressure) than patients who have virological failure without resistance. Further analysis showed that, in the dolutegravir group, viral suppression was achieved by a greater proportion of patients who were switched to WHO-recommended NRTIs (158 [87%] of 182 participants) than those switched to other second-line NRTIs (103 [79%] of 130).[4] This result shows that residual NRTI activity also contributes substantially to efficacy of dolutegravir-based regimens, corroborating the importance of optimising the second-line NRTI backbone in accordance with the WHO algorithm.[3]

The introduction of dolutegravir in many low-income and middle-income countries (LMICs) offers great potential for improved ART outcomes and tolerability at a lower cost.[7] However, data from DAWNING and other studies raise several important unanswered questions about the risks of emerging dolutegravir resistance in LMICs. First, in DAWNING,[4] integrase resistance mutations were detected in two of the 11 participants with virological failure (defined as HIV-1 RNA ≥400 copies per mL) in the dolutegravir group; the emergent Gly118Arg integrase mutation was identified in two participants with virological failure who had NRTI resistance (Lys70Glu plus Met184Val or Met184Val plus Lys219Lys or Lys219Glu) at study screening and who were started on lamivudine plus emtricitabine plus zidovudine or tenofovir as second-line NRTI backbone.[4] Emergence of Gly118Arg might be facilitated by a natural genetic polymorphism with a low genetic barrier at codon 118 in non-B HIV subtypes, which is particularly worrying because it is associated with clinically significant (at least 13-fold) resistance to dolutegravir.[8] Second, this raises the additional concern that pre-existing NRTI resistance might reduce effectiveness and durability of dolutegravir-based second-line regimens. Notably, one in ten of screened patients had extensive NRTI resistance with no active NRTIs (and they were therefore excluded from trial participation). In real-world settings, where NRTI resistance might be even more common, unknowingly starting such patients on functional dolutegravir monotherapy could be a harmful strategy, as has been shown by dolutegravir maintenance monotherapy trials.[9,10] Third, these risks might be further exacerbated given that access to and functional use of viral load tests (for accurate detection of virological failure) is still scarce in many settings, and that the ability to perform genotypic resistance testing to optimise the NRTI backbone (as was done in DAWNING[4]) is non-existent in most LMICs.

Many LMICs are transitioning millions of patients to first-line dolutegravir-based ART.[11] If more people might develop integrase resistance over time, there is

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.

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I declare no competing interests.

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Clostridium difficile infection trials: what is the primary endpoint?

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See **Articles** page 265

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