

Pan-resistant HIV-1: what's next?



In *The Lancet Microbe*, Maria C Puertas and colleagues¹ report the first well documented clinical case of a male patient infected with a pan-resistant HIV-1 subtype B strain, which showed broad genotypic and phenotypic cross-resistance to all approved oral antiretrovirals from five drug classes, including the widely used second-generation integrase strand transfer inhibitor (INSTI), dolutegravir. The most recently approved drugs (in 2018), doravirine (a next-generation non-nucleoside reverse-transcriptase inhibitor [NNRTI]) and bictegravir (an INSTI), would be impeded by the pre-existing drug resistance mutations in reverse transcriptase (doravirine) and integrase (bictegravir) coding regions. This highly treatment-experienced patient acquired the complex pan-resistant HIV-1 strain over the course of 28 years of antiretroviral therapy (ART), following initial exposure to suboptimal therapy, poor viral suppression to subsequent potent regimens, and current virological failure on a dolutegravir-based regimen. Although the patient regularly attended his clinic visits and had no recorded mental health problems, no further details were provided regarding the underlying causes of the patient's dire situation, such as any challenges around medication adherence, the adequacy of plasma drug concentrations, the occurrence of adverse drug effects, or any behavioural or social issues. Appreciating the individual patient's sociocultural context is an important prerequisite for achieving long-term HIV treatment success.

To date, clinical reports of five-class multidrug-resistant HIV-1 are scarce. The first reported case was of a man with advanced disease who had received treatment for 18 years and who had received an experimental salvage regimen, which included the anti-CD4 monoclonal antibody, ibalizumab, with limited success.² The second case was an antiretroviral-naïve individual who provided the first evidence of the transmission of a HIV-1 variant with resistance to five drug classes.³ Furthermore, the TMB-301 ibalizumab trial⁴ included five patients who carried viruses that were resistant to all approved antiretroviral drugs at time of study enrolment (2015–16), although no genotypic or phenotypic data were reported in this study.

Together, these cases provide evidence that multidrug cross-resistance remains an important clinical concern,

despite the extensive number of treatment options available in the current ART landscape. These cases also underline the need for the continuous discovery of new drugs with new mechanisms of action, and the inclusion of highly treatment-experienced patients in clinical trials.

Of note, Puertas and colleagues¹ did ultrasensitive resistance genotyping by next-generation sequencing, which is an emerging powerful diagnostic tool that can improve the ability to detect drug-resistant minority variants archived in the patient's latent viral reservoir. This method could help to improve the prediction of drug susceptibility by identifying the lowest concentrations of drug-resistant minority variants that still have clinical relevance.⁵ Ultrasensitive resistance genotyping might therefore be particularly useful for heavily pretreated patients whose drug resistance history is unknown or not well documented, to help identify archived drug-resistant minority variants and enable accurate selection of the most effective drug regimen.

Puertas and colleagues¹ make a valid point that insufficient data are available about the epidemiology of multidrug-resistant HIV infections globally and about the effects that these infections have on public health, highlighting the need for robust global drug resistance surveillance systems that continuously inform treatment guidelines.^{6,7} The emergence of HIV drug resistance following the rollout of life-saving ART to millions of people in low-income and middle-income countries (LMICs) remains an important threat to ending the global HIV epidemic, and risks compromising individual outcomes and increasing onward transmission. Triple-class drug-resistant HIV-1 strains, which are resistant to nucleoside reverse transcriptase inhibitors, NNRTIs, and protease inhibitors, have already been reported in treatment cohorts in LMICs, particularly among children and adolescents.⁸ In addition, a number of cases with resistance to all four classes of antiretrovirals available in LMICs have already been reported in sub-Saharan Africa, meaning that these cases are essentially untreatable in this context.^{9–12} These cases include one individual in Zimbabwe¹¹ and one individual in Botswana,¹⁰ both of whom had virological failure to a salvage regimen containing ritonavir-boosted

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darunavir and dolutegravir after previous exposure to raltegravir. The third individual was a perinatally infected adolescent in South Africa who had virological failure on a salvage regimen containing raltegravir, and who had dolutegravir cross-resistance mutations.¹² A 2019 study done in South Africa reported three patients with intermediate-to-high level dolutegravir resistance, two of whom had been exposed to raltegravir, and the remaining patient had been exposed to a salvage regimen containing dolutegravir.⁹

The magnitude of the impact that emerging multidrug-resistant HIV could have on public health is a function of the number of available therapeutic options, with the important caveat that HIV treatment is a lifelong intervention. There is thus a strong imperative for LMICs to safeguard the limited number of available drug options, especially among groups that are most at risk of multidrug resistance. The recent (2018) recommendation to use dolutegravir in both first-line and second-line treatment regimens in LMICs reflects major progress towards improving long-term treatment success and helping address the challenge of the high prevalence of pretreatment drug resistance to NNRTIs in many settings.⁷ Nonetheless, a strong preventive framework is needed to ensure that large-scale multidrug resistance will be avoided.⁶ Robust patient-centred care models are crucial for delivering high-quality services to people living with HIV over their lifetime, and across diverse health systems and contexts. These care models include the use of simple, highly potent regimens, close individual viral load monitoring, and improved attention to mental health and adherence challenges, especially in populations that are most at risk of multidrug resistance, such as children and adolescents.⁶

We declare no competing interests.

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*Raph L Hamers, Seth C Inzaule
raph.hamers@ndm.ox.ac.uk

Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK (RLH); Eijkman-Oxford Clinical Research Unit, Jakarta 12430, Indonesia (RLH); and Department of Global Health, Amsterdam Institute for Global Health and Development, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands (RLH, SCI)

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