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## **HIV drug resistance in resource-limited countries: Threat for HIV elimination**

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Nearly 22 million people living with HIV worldwide are now receiving antiretroviral therapy (ART). To achieve the UNAIDS goal of eliminating HIV as a public health threat by 2030,<sup>1</sup> ART coverage should be maximised, its continued efficacy closely monitored and steps taken to prevent treatment failure. HIV drug resistance (HIVDR) represents one of the major dangers that should be carefully investigated and adequate responses to recognise, adapt treatment and to prevent the development of resistance implemented.<sup>2</sup>

The study by Chimukangara and colleagues, published in this issue of *EClinical Medicine*, investigated trends in the prevalence of pretreatment HIVDR (PDR) in South Africa (SA), between 2000 to 2016.<sup>3</sup> The authors report an overall PDR prevalence of 6.9%, and more importantly, a 1.10-fold yearly increase in the odds of PDR. This finding is consistent with other recent reports of an alarming increase in PDR in the Sub-Saharan Africa region.<sup>4</sup> These results clearly show that the expansion of ART programs initiated in the 2000s in SA as in many other resource-limited countries (RLC), fueled the emergence of HIVDR and its subsequent transmission.

The major strengths of the Chimukangara et al. study include the context, SA ART program is the world largest ART program, as well as the large sample size, with the analysis including up to 6880 reverse transcriptase and 6294 protease sequences. Their results highlight one of the major limitations of the public health approach. Indeed, while this approach has permitted the rapid expansion of ART in RLCs, the associated rapid and ongoing increase of PDR and acquired drug resistance (ADR) in patients on ART, are of critical concern. High levels of ADR favor PDR and recent studies from RLC reported high levels of virological failure, up to 30%, in populations on first-line ART, and rapid development of HIVDR.<sup>5,6</sup> Low adherence to treatment,

inadequate virological monitoring and other program-related factors such as drug stock-outs are associated with virological failure and the emergence and accumulation of resistance mutations.<sup>7</sup> In addition, as mentioned by Chimukangara and colleagues “long delays in switching people with virological failure to second-line regimens” increase the probability of transmitting a resistant virus.

As ART coverage in RLCs expands, detecting, combating, and preventing HIVDR and especially PDR, must necessarily become a growing priority. The routine monitoring of viral load (VL) is expected to improve ART outcome and should also support prevention of HIVDR.<sup>8</sup> In addition, VL monitoring is cost-effective, by preventing premature introduction of more costly second-line regimens, and also by reducing the need of drug resistance testing for second-line ART initiation. Therefore, strengthening the routine use of VL monitoring in RLC is essential. However, as mentioned by Chimukangara and colleagues, SA already has an effective VL monitoring program, which begs the question of what other factors may need to be considered to limit HIVDR ?

The use of drugs with a low genetic barrier to resistance, especially the NNRTIs drugs such as nevirapine and efavirenz, is associated with selection and transmission of NNRTI-resistant viruses. Since 2017, the WHO has recommended non-NNRTI first-line ART regimens in countries where NNRTI PDR exceeds 10%.<sup>9</sup> The study from Chimukangara and colleagues supports this recommendation in SA. Also, as we now know that NNRTI PDR inevitably increases in programs using NNRTIs and represents a serious risk for ART outcome, NNRTI-free regimens should be considered in all RLCs. The WHO recommends transition to a dolutegravir (DTG)-based first-line regimen when safe for the patient, but that is not enough. In fact, Chimukangara and colleagues work also highlight the increase of NRTI PDR,

especially TDF-associated resistance, which is consistent with recent studies from RLC.<sup>10</sup> A reasonable expectation is that TDF resistance will soon represent a serious threat and a similar scenario cannot be excluded for DTG, even though its barrier to resistance is higher.

Major limitations of the study include the fact that the true ARV status of participants is uncertain, and previous exposure to ARV for some of the study participants cannot be excluded. Also, it is essential to assess PDR in other populations, especially pediatric populations.

In conclusion, combined with similar data from RLCs, the study by Chimukangara and colleagues points to a growing threat of HIVDR and PDR endangering ART efficacy and goals for HIV elimination. It is clear that new strategies are needed to prevent HIVDR in RLC and perhaps it is time to reconsider the public health approach and start moving toward patient-centered strategies for HIV care and treatment in SA and in other RLCs.

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