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Commentary

# Following the path: Increasing trends of HIV-1 drug resistance in China

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The emergence of the primary and acquired drug resistance mutations (DRM) poses a significant threat to successful antiretroviral therapy (ART) against HIV-infection. The WHO/UNAIDS 90–90–90 targets [1] are that 90% of the people living with HIV (PLHIV) know their HIV-status, and, of them, 90% are accessing therapy; finally, of those who are accessing treatment, 90% should have suppressed viral loads. The success of this strategy highly depends on the prevention and monitoring of the pretreatment drug resistance (PDR) and acquired drug resistance (ADR). Monitoring the population-level emergence of HIV drug resistance (HIVDR) is essential to limit the premature treatment failure and further transmission of HIVDR to newly infected patients. For decades the typical choice for the first-line ART combinations has included two nucleoside reverse transcriptase inhibitors (NRTIs) with non-nucleoside inhibitors (NNRTIs). The NNRTI is generally replaced with boosted protease inhibitors (bPIs) as second-line treatment. The 2019 WHO HIV drug resistance report indicated that in 12 out of 18 countries where the pre-treatment HIV drug resistance (PDR) survey was conducted between 2014 and 2018, the level of the PDR to NNRTIs among adults initiating first-line ART exceeded 10% mainly from African regions, regions of America and even in western pacific country Papua New Guinea and Nepal in Asia. [2]. Though studies from Asian countries have shown TDR below 10% [3], recent studies from India have reported an increase in TDR to moderate levels indicating a rise in HIVDR [4]. The rise in HIVDR in the Asian region is supported by a recent meta-analysis showing a substantial annual increase in NNRTI resistance [5].

The Chinese Government initiated free ART access to PLHIV in 2003. Since then, there were rapid scale-up of the access to the therapy. In this article of *EClinicalMedicine*, Zuo and colleagues [6] conducted a systematic review and meta-analysis of HIVDR including data that had been reported in English and Chinese between 2001 and 2017. They have reported a pooled prevalence of TDR at 3%, while ADR prevalence was 44.7%. Though the overall prevalence during that period was low, there were increasing temporal trends of HIVDR from 4.75% in 2001 to 6.25% in 2017, in treatment naïve individuals. The significant increase of DRM was for NNRTI (2.25% in 2001 to 5% in 2017), while NRTI and PIs were stable. The prevalence of HIVDR was proportionate with the coverage and duration of access to the ART. Central China had a higher coverage [7], and a longer period of access to ART [8] coincides with the observed higher HIVDR rate that crossed the 10% threshold. This can further impact the epidemic by increasing the risk of transmission of HIVDR in treatment naïve individuals in the population. Furthermore, the Central China showed distinct mutation profile compared to North and South China that was supported by phylogenetic analysis. The frequently observed mutations M184V/I (NRTI) in treatment experienced individuals and M46I/L (PI) in treatment naïve individuals from North and South China were rarely observed in Central China and a high percentage of K103N/S mutation was observed in treatment naïve sequences of Central China. Substantial evidence supports the impact of genetic diversity on ART responses and drug-resistance pathways. RT mutation V106M confers resistance to most NNRTIs, and it is more prevalent in HIV-1C and 01_AE than HIV-1B [9] also observed by Zuo and colleagues. In CFR01_AE, a high percentage of PI mutation M46IL occurred while in HIV-1B, it was reverse transcriptase inhibitor mutations (M184VI, K103NS, and Y181CI). It is important to note that the high proportion of M46IL mutation observed in CRF01_AE could be due to transmission as opposed to be a natural polymorphism in other subtypes.

In summary, the comprehensive meta-analysis from China replicated the global trends of the alarming increase of HIVDR, which needs a closer look. As the authors advocated for the reassessment of the use of 3TC, EFV and NVP, the most important will be to increase the frequency of the viral load monitoring at least in the first two years after initiation of therapy and appropriate adherence counseling. Earlier studies from the region echoed the pattern of poor adherence [10] that was observed in the LMICs where the public health approaches for HIV-treatment were implemented. The frequent viral load testing will not only act as a proxy to adherence, but it will also identify early viral failure, thus the emergence of HIVDR and option to adherence counseling to the non-compliance patients. A regional pretreatment drug resistance could also be an option given Central China has crossed the 10% mark. Besides, WHO guidelines for the treatment of PLHIV recommended the rapid adaptation of dolutegravir (DTG) based regiments as the preferred first-line treatment. However, DTG based regiment without viral load monitoring and suboptimal adherence may end up in a similar increase of HIVDR in the near future.

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## Declaration of Competing Interest

None

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