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HIV drug resistance to integrase inhibitors in low- and middle-income countries

Dolutegravir (DTG)-based antiretroviral therapy (ART) is the cornerstone of HIV treatment in low- and middle-income countries (LMICs), recommended by the World Health Organization (WHO) for use in both first- and second-line treatment. This follows evidence from clinical trials showing better efficacy and safety when compared with previously recommended regimens[1]. DTG-based ART has led to an increased number of people living with HIV achieving viral suppression, raising hope that the epidemic control can be attained. Failure of DTG treatment was rarely accompanied by the emergence of drug resistance mutations in clinical studies of ART-naive populations[2,3]. Clinical trials conducted over 48–96 weeks showed very low risks (0.1%) of emergent resistance on first-line treatments, and low rates (0.6–3.8%) of emergent resistance on second-line DTG-containing regimens, with higher risks in children and settings in which ART selection was not guided by genotyping[2]. Although these findings are encouraging, they show that without adequate monitoring, there might be an earlier selection of DTG resistance, especially for those who transitioned or switched to DTG without viral suppression[1]. Surveillance of integrase strand-transfer inhibitor (INSTI)-associated mutations in LMICs that are transitioning to DTG-containing regimens is needed to monitor virological failure and acquired DTG resistance in routine clinical settings.

A recent review assessing DTG resistance among INSTI-naive individuals in 36 studies globally identified 99 individuals with resistance. Of these, 49.5% were on ART and receiving DTG plus two nucleoside reverse-transcriptase inhibitors (NRTIs), 11.1% were on ART (with viral suppression) and had switched to DTG monotherapy, 15.2% were ART-naive viremic individuals receiving DTG plus two NRTIs or DTG plus 3TC, and 24.2% were receiving other ART combinations. The study identified four major pathways of DTG resistance: R263K (n = 40); G118R (n = 24); N155H (n = 9); and Q148H/R/K (n = 9). Phenotypic data have shown that these mutations affect DTG efficacy; in terms of resistance, R263K, Q148HRK and N155H lead to a 2.0-, 1.4- and 0.8-fold reduction in DTG susceptibility if considered alone[4–6]. At the same time, the mutations also affect viral replication. At the time of writing, G118R has the highest impact in decreasing integration activity and replicative capacity[4].

The combined (although opposite) effects of these mutations via increased resistance and decreased replicative capacity, might help to explain the reduced rate of resistance found in patients treated with DTG-based regimens. However, this protective effect tends to wane over time in cases of prolonged virological failure during treatment with DTG-based regimens. Data presented at the 30th International Workshop on HIV Drug Resistance and Treatment Strategies revealed growing rates of drug-resistant mutations associated with acquired resistance to DTG among patients from several countries globally[2,7]. In current routine clinical practice[8], emergent DTG resistance is being gradually detected in different case scenarios of patients experiencing virological failure, including after transitioning from an NNRTI-based first-line regimen without consideration of viral load in the presence of K65R and M184V; after a treatment switch in heavily treated cases with multi-drug resistance to both protease and reverse transcriptase inhibitors; and after concomitant treatment with DTG and antituberculosis drugs[9]. The growing emergence of DTG resistance underscores the need for cautious and careful use of this highly potent drug.

Several lessons can be drawn to support global efforts for the long-term sustainability of ART success in the DTG era[10]. Scaling-up of the monitoring of viral load is essential to quickly identify patients with adherence challenges who should be offered intensified adherence counselling, and in case of virological failure after a second-viral load test, rapid switch to next-line of treatment. Scale-up of the testing of viral loads can leverage low-cost point-of-care tests and networks of centralized laboratories for field operations in LMICs. Affordable point-of-care adherence monitoring tests, with the capacity for facility-based and community-based testing of adherence to DTG-containing regimens or tenofovir levels in urine[10], should also be more widely used to prevent unnecessary treatment switches.

For individuals on DTG-based regimens with a confirmed virological failure, providing point-of-care drug resistance testing and rapid switching in case of DTG resistance after adherence counselling can prevent prolonged viremia. The logistics for genomic surveillance set up during the COVID-19 pandemic in several LMICs, including through the support of Africa CDC pathogen genomics initiative as well as other partners, can be converted to testing of HIV drug resistance, targeting specific viral genes for optimization of ART-combinations after failure on DTG-containing regimens[4,5]. This pivot may in some settings require a shift from first-generation Sanger-based sequencing to second-generation Illumina-based sequencing (which produce shorter reads), or third-generation nanopore-based sequencing devices (which produce long reads); costs can be reduced through multiplexing of several samples[5]. Nanopore technology requires minimal maintenance and is widely available in LMICs and so would be cost-effective for both individual HIV drug-resistance testing and programmatic surveillance of DTG efficacy[4,5].

To overcome adherence challenges and the growing burden of drug resistance, long-acting antiretrovirals might become a game changer in sustaining long-term virological success. However, there have been reports of virological failure, due to drug resistance to long-acting cabotegravir and rilpivirine, after only two or three years of treatment. This calls for a careful selection of people eligible for long-acting ART in LMICs, where NNRTI-based regimens have been widely used in the past, as there may be cross-resistance[5,10]. Resistance to long-acting ARTs in LMICs might be best reduced by combination treatment with INSTI (cabotegravir or bictegravir) and capsid inhibitor (lenacapavir)[5,10].

Implementation of the current ART strategy also requires an effective system for reporting on pharmacovigilance, taking into consideration the potential weight gain and risks of cardiovascular diseases with

the recommended combination therapy (DTG–tenofovir–lamivudine)[1], and risks of gluteal subcutaneous cold abscesses from long-acting injectable antiretrovirals. Patient perceptions and patient-reported outcomes should also be considered to ensure acceptability, efficacy and maximal benefits of long-acting antiretrovirals.

DTG-based ART will continue to contribute to achieving the 95–95–95 targets for HIV. However, sustaining these gains will require better treatment-monitoring strategies, including viral load and therapeutic drug monitoring tests, as well as enhanced genomic surveillance[10]. These measures will be crucial for eliminating AIDS as a pandemic in LMICs by 2030.

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