Next-generation sequencing and HIV drug resistance surveillance

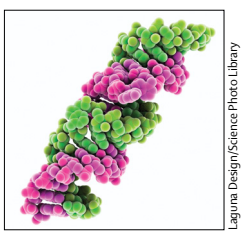
Circulating drug-resistant HIV-1 variants in antiretroviral-naive populations are on the rise in regions where access to antiretroviral therapy (ART) has recently been scaled up, particularly in low-income and middle-income countries (LMICs).[1,2] This increase threatens the success of national ART programmes and the achievability of the UNAIDS 90-90-90 treatment goals for AIDS.[3]

In *The Lancet HIV*, Ávila-Ríos and colleagues[4] present findings from a 2015 nationally representative survey of antiretroviral-naive patients with HIV in Mexico, reporting high levels of HIV drug resistance, with about 10% of individuals having viruses resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs). The Achilles' heel of NNRTI-based regimens is their low genetic barrier to resistance and the replication capacity of resistant variants.[5] Nonetheless, because of low costs and high antiviral efficacy (in the absence of resistance),[6] first-generation NNRTIs are expected to remain the cornerstone of first-line therapy in LMICs for the foreseeable future. In Ávila-Ríos and colleagues' study,[4] the presence of resistance before ART was associated with a four-fold increased risk of virological failure within the first year of ART. This worrying finding adds to a growing body of evidence from a broad range of settings that has quantified the effect of resistance in terms of impaired virological and immunological response to first-line therapy, further acquisition of drug-resistance mutations in patients failing therapy, and the increasing need for switches to costlier second-line and third-line therapies.[7–10]

Ávila-Ríos and colleagues' study is a commendable effort to adopt the latest WHO guidance for nationally representative surveys of HIV-drug resistance.[11] The study findings suggest that national ART programmes in LMICs should invest in efforts to minimise the development of resistance, mainly by ensuring uninterrupted drug supply, adequate adherence support, access to routine viral-load monitoring, and access to alternative drug regimens. The findings will also fuel debate among national policy makers and global HIV agencies about what additional actions are needed to sustain optimum ART outcomes, including the need and feasibility of resistance genotyping for management of patients. Of note, growing numbers of patients in LMICs who enrol in ART programmes have previously been exposed to antiretroviral drugs, increasing their risk of carrying drug-resistant HIV and subsequent virological failure.[7] Therefore, by contrast with the present study, which excluded patients who reported any previous use of antiretroviral drugs, WHO explicitly recommends inclusion of this high-risk group in population-based surveys of pretreatment resistance.[11]

One of the items that the investigators explored in their study was the potential of next-generation sequencing to facilitate surveillance of HIV-drug resistance. The study confirmed a dose–effect association between the level of low-abundance NNRTI-resistant mutants and virological outcomes, and suggested a 5% threshold of mutant frequency for clinical relevance. However, the ability of this study to assess if even rarer variants (1–5%) could still affect clinical outcomes was limited by the few additional NNRTI mutants detected with next-generation sequencing and the short follow-up after NNRTI initiation (median 9·4 months), meaning that the effect of low-abundance NNRTI variants on viral rebound after achieving suppression is largely unexplored.[12]

Next-generation sequencing provides great potential in the medium-term to long-term, because it brings together technical non-inferiority and even superiority compared with Sanger (or first-generation) sequencing at a substantially lower cost per test in centralised high-throughput laboratories.[13] Cumulative evidence that low-abundance transmitted NNRTI-resistant variants affect the outcomes of first-line NNRTI-based therapy[14] highlights the added benefit of ultrasensitive HIV-genotyping methods for resistance surveillance. The limitations of next-generation sequencing are the high-level expertise and expensive bioinformatics support required for data analysis; however, streamlined robust, low-cost, and low-complexity bioinformatic analysis pipelines are being developed, which will enable expanding access to HIV next-generation sequencing. To increase their utility for LMICs, the strengthening of centralised high-throughput laboratories, including efficient systems for sample referral and results distribution, as well as regional hubs for bioinformatics will be crucial to increase the economies-of-scale while reducing costs.[13]



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In conclusion, investments in the global HIV response should emphasise sustained viral suppression with ART not only to improve survival and reduce HIV transmission, but also to prevent large-scale HIV-drug resistance.

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