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Commentary

HIV drug resistance testing – The quest for Point-of-Care

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The fight against a Human Immunodeficiency Virus (HIV) pandemic is progressively advancing towards the ambitious 90-90-90 goal: to diagnose HIV infection in 90% of infected subjects, provide treatment to 90% of those and, finally, achieving viral suppression in 90% of treated patients. On this path towards eradication, strong epidemiologic surveillance mechanisms have warned of an increase in HIV resistance to the common antiretroviral treatments (ART), which affects more than 10% of the infected population in low- and middle-income countries (LMICs) [1]. Updated guidelines recommend changing one of the three drugs that usually conform ART, for Dolutegravir (DTG) [2]. However, DTG efficacy may also be at stake when a patient's virus is already resistant to the ART drug backbone, and represents a possible source of future resistant DTG that undermines efficacy of integrase inhibitors drugs.

Clinically, HIV resistance is managed differently in LMICs compared to high-income countries. In LMICs, ARTs are designed according to a public health approach that is not guided by viral genetic information but by patient clinical course. Conversely, in richer countries, a Sanger-based genetic test is performed on every patient's viral genome, inferring drug resistance from genotypic information and taking advantage of the large genotypic to phenotypic knowledge base [3]. Unfortunately, despite ART resistance being specific to LMICs, the cost of standard HIV drug resistance testing (DRT) is too high for LMICs to adopt [4]. Thus, there is an urgent need to build cost-effective DRT alternatives that overcome high cost, long turn-around times, HIV genetic diversity, supply chain discontinuity and sample type heterogeneity.

Two main alternatives exist. Next Generation Sequencing-based approaches for high throughput HIV DRT pipelines can benefit from the extremely low cost per nucleobase and cloud-based data analysis [5]. However, their potential in generating affordable clinical grade DRT results and almost real-time epidemiological information relies on centralizing testing in large platforms, thus increasing time to clinically actionable results and hampering its applicability in LMIC contexts.

Alternatively, Point-of-Care (PoC) technology aims to overcome these limitations by creating cheap single-use devices to provide decentralized clinical grade DRT results. For HIV DRT, development of PoC devices orbits around Point Mutation Assays, designed to detect a handful of specific mutations that are relevant for HIV resistance clinical management [6]. PoC reduces the need for lab equipment to a minimum while shortening time to results and cost per sample, with the tradeoff of missing whole HIV genetic sequence information and derived epidemiological information.

Several research efforts have recently proven technical viability but many have not been developed further. Most promising technologies rely on the careful design of primers that are specific to resistant mutations positions in the HIV genome. Oligonucleotide Ligation-based Assay (OLA) derived assays use a DNA amplification procedure using three probe-ligated primer sets. These are specific for mutations with high clinical relevance, allowing naked-eye distinction between mutant and wildtype HIV variants on a coated plate or paper strip [7]. On the other hand, Pan-degenerate Amplification and Adaptation (PANDAA) technology is based on quantitative PCR (qPCR) taken to the limit, using extremely degenerate primers that target specific mutation sites and can cope with high HIV diversity next to mutation site [8]. PANDAA shows high specificity and sensitivity and can reproduce drug resistant mutation frequency obtained from NGS data with high accuracy, although the need for a qPCR instrument remains a challenge for broad adoption.

In this issue of *EBioMedicine*, Panpradist et al. present a further development of their previous CLIA-OLA method; a significant step towards tangibility of OLA-based HIV PoC DRT [9]. Authors built OLA-Simple, a miniaturized version built from the thorough experimental evaluation of several reactants, buffers and enzymes to minimize lab requirements to standard equipment, reducing time to results and per-sample cost. To test OLA-Simple PoC, authors selected diverse leftover sample types, from different origins and subtypes, and carefully designed a human testing setup to mimic the real setting where OLA-Simple will need to be used. Generated knowledge is translated into the development of an assistant software that guides users through the process and interprets results automatically.

Importantly, in the work of Panpradist et al., PoC testing is conceptually described as a whole, comprising technology and context. Not only the complex molecular biology machinery is craftfully embedded and tested within a single use, low cost device, but also assayed and validated in a close-to-real context, putting it to use by

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inexperienced users that are guided by ad hoc created companion tools in carefully designed feasibility tests. Of note, ad hoc mobile software not only increases test robustness and usability but may also be an entry point to controlled data collection for surveillance. While such PoC technology deployment into a real-world setting faces challenges such as materials, continued supply, and cold chain maintenance that demand operational research and cost-benefit studies [10], work by Panpradist et al. represents an important step forward for HIV drug resistance testing.

Declaration of Competing Interest

None.

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