

## Editorial

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# The Need for a New Generation of HIV Diagnostics

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Despite remarkable advances in the prevention and treatment of HIV, over 35 million individuals currently live with active HIV infection and worldwide, there were nearly 2.1 million new cases of HIV in 2013.<sup>1,2</sup> The benefits of rapid testing to determine HIV infection are well established - the introduction of Highly active antiretroviral therapy (HAART) treatment within four hours of exposure has been shown to dramatically limit both virus spread and progression to AIDS.<sup>3</sup> Equally critical is the need to continuously monitor virus load in individuals on HAART and/or other HIV therapies. With the expansion of HAART in countries with poor access to and/or quality of health care, individual variations in HAART effectiveness may be infrequently monitored. Negative outcomes of this well-intended expansion may be that individuals on HAART assume they are either virus-free or incapable of spreading infection - whereas the opposite status would have potentially tragic outcomes. Lastly, as we look to the future and the implementation of HIV vaccines, the capacity to monitor virus directly, not just the presence of antibodies to HIV, is increasingly critical.

Diagnostic tests to detect HIV based on the presence of circulating antibodies are portable, relatively rapid and low cost (e.g., OraQuick In-Home HIV Test \$40USD) and are thus suitable for in-home use. However, these tests have inherent limitations. First, as the presence of antibodies to HIV requires an inductive phase of immune activation, which may vary among individuals, these kits cannot reliably measure HIV infection until weeks after initial contact. Second, these tests are not quantitative. Third, such assays are not suitable for monitoring the status of chronic HIV infection, as antibodies to HIV are constitutively present at high levels. Lastly, while such kits may have utility in measuring the induction of an immune response to HIV vaccines, they are not suitable for assessing virus infection in individuals who may have received such a vaccine. Traditional approaches to directly measure the presence of virus, by DNA/RNA based PCR or by ELISA methods, are quantitative and characterized by high sensitivity (50 particles/ml and 3.5 pg/ml respectively). Unfortunately, these tests require relatively sophisticated accompanying infrastructure in the form of access to a health clinic or diagnostic lab, and accordingly they are more expensive (\$100-300USD per assay) and restrictive to use.

As a result, even patients with access to excellent care are often monitored infrequently, and many HAART subjects with limited access to health care professionals are simply not monitored at all. Alere Inc. has marketed a more recent improvement on these approaches in the form of both a point-of-care HIV antibody/p24 antigen test (Alere Determine™ HIV-1/2Ag/Ab Combo) and of a self-contained PCR-based screening method/device for use in local clinics (Alere™ q HIV-1/2 Detect). While these constitute important advances in both diagnostics and care, the need remains for a point-of-care test that is both quantitative and affordable.

In summary, while each of the approaches noted above offer advantages, none achieve the desired ultimate goal of direct virus measurement using a low cost, point-of-care device that is sensitive, quantitative and, when desired, directly linked to a health care professional for follow on decisions. This analysis also suggests that continued refinement of assays based on the

traditional molecular technologies of ELISA, Western blot and PCR are likely not viable solutions.

Recent progress in micro-electronics and micro-mechanical fabrication technologies opens exciting possibilities for the development of a new class of devices to measure chemical and biological elements.<sup>4</sup> High frequency Bio Nano Sensors (BNS) are small microchip size, solid-state devices with disk, plate or prism shapes that are implanted with a system of metal electrodes used for interfacing the sensor with electronic circuits. They are label-free, inexpensive, portable and simple to use, and can sense gases, fluids and solid materials with high accuracy and reproducibility. BNS are thus well suited for applications in analytical labs as well in point-of-care settings. Among several BNS detection systems, piezoelectric high frequency technology provides a particularly attractive platform. These devices are compatible with integrated circuit, and micro and nanoelectromechanical systems, show excellent aging characteristics, and are capable of measuring multiple components in one sensor package. Sensors based on this technology can be manufactured using standard photolithography and are relatively inexpensive to produce.

Piezoelectric sensors function as resonant electromechanical units that can be excited at their fundamental and harmonic frequencies to generate acoustic waves having different penetration depths. This sensing attribute provides the distinctive capability of 'slicing' biological interfaces simultaneously at different depths, thus improving selectivity, sensitivity and reliability during detection. Of the many types of piezoelectric sensors several have also been developed for medical applications, including the use of immunosensors in which antibodies or antigens are immobilized on the sensor surface.<sup>5</sup> Examples of this approach include the measurement of virus and virus antibodies, including herpes virus, hepatitis virus, swine fever virus, and at least in one indication the measurement of HIV-1/2 with both specificity and speed.<sup>6</sup>

In conclusion, it's time for health care workers and virologists to look increasing to technologies resting classically in the domains of physics, engineering and information technology to advance new approaches to HIV diagnostics - ones that no longer rely on either the historical business model of laboratory medicine or approaches of molecular medicine. While BNS need to improve both in the sensitivity of detection and the miniaturization of component parts, this technology holds great promise for a markedly new approach to HIV diagnostics and care. In theory, BNS technology also enables the simultaneous measurement of multiple parameters of health status beyond the level of antibody and virus, such as CD4 counts. These measurements when conducted at home or in local clinics could then be electronically linked to a health care professional ushering in a new era of remotely managed integrated health care.

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