Earlier HIV detection with prototype Abbott assay

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June 2019—Abbott unveiled a new and improved fourth-generation prototype HIV assay at the 2019 HIV Diagnostics Conference in March.

In an Abbott-funded study, the prototype assay was compared with the fourth-generation Abbott Architect HIV Ag/Ab Combo and Roche Elecsys HIV Combi PT run on the Cobas e602. It demonstrated broad detection of HIV-1 and HIV-2 genotypes with enhanced p24 analytic sensitivity and a reduction of the seroconversion window. The prototype assay was also found to have high specificity with minimized heterophilic antibody interference.

'This fourth-generation prototype assay is designed to detect highly infectious people who may be missed by existing tests.' Xiaoxing Qiu, PhD

Xiaoxing Qiu, PhD, a key developer of the prototype, presented data evaluating the performance of the prototype against current on-market Architect and Elecsys assays with the WHO International HIV-1 p24 standard, 14 commercial seroconversion panels, and an antigen-positive panel composed of four specimens from acute HIV-1 infections and 17 genetically diverse HIV-1 and HIV-2 virus isolates. The comparative evaluations took place at Abbott and in the Department of Pathology, Johns Hopkins Medical Institutions.

The analytic sensitivity of the prototype assay (0.20 IU/mL) was fourfold better than those of the Architect (0.80 IU/mL) and Elecsys (0.86 IU/mL) assays with the WHO p24 standard, said Dr. Qiu, who is a research fellow, Volwiler Society, Infectious Disease Research and Product Development, Abbott.

"Studies have demonstrated that a fourth-generation test such as Architect HIV Ag/Ab Combo can detect up to 83 percent of acute HIV infections missed by third-generation antibody-only assays," Dr. Qiu tells CAP TODAY. "The fourfold increased analytical sensitivity of Abbott's new, improved prototype assay suggests this assay can detect a higher percentage of acute HIV infections relative to Architect and Elecsys."

John R. Hackett Jr., PhD, divisional vice president, Abbott Applied Research and Technology, attributed the higher sensitivity to a combination of factors, one of which is a redesign of the recombinant proteins used to drive the assay performance.

Says Dr. Qiu: "Maintaining antigen detection sensitivity for genetically diverse HIV strains is dependent upon the quality of monoclonal antibodies used by fourth-generation tests. For improving detection of HIV-2 antigen, we

selected the monoclonal antibodies recognizing highly conserved epitopes between HIV-1 and HIV-2."

Originally, she says, a biotin-streptavidin capture method was used to improve the prototype's sensitivity. After the Food and Drug Administration issued its safety warning in 2017 about biotin interfering with laboratory results, "we redesigned the prototype without using the biotin-streptavidin capture method."

In the evaluation of the assay's ability to detect diluted HIV-1 antigen genotypes, the prototype assay "demonstrated enhanced analytical sensitivity across all 15 HIV-1 strains, including the highly divergent group N, P, and O isolates," Dr. Qiu says. The enhanced antigen sensitivity (1.6–5.3-fold) suggests the assay is "designed to offer the best-in-class fourth-generation test for detection of acute infection from divergent HIV strains."

Cases of several diverse HIV strains escaping detection in fourth-generation tests have been reported, she says. "Studies also demonstrated that the antigen sensitivity of some fourth-generation and antigen-only tests was impacted by HIV genetic diversity, particularly with HIV-1 non-B subtypes."

The prototype assay also outperformed the Architect and Elecsys assays in detecting HIV-2 antigen subtypes. The sensitivity of the prototype assay was more than 10-fold higher than that for the Elecsys assay and more than 100-fold higher than that for the Architect assay. "Although clinical utility of HIV-2 antigen remains to be discovered because acute HIV-2 infection is rarely identified, the prototype assay may help improve detection of acute HIV-2 infection as this test detects the HIV-2 p26 protein, as well as antibodies to HIV-2," Dr. Qiu says.

The seroconversion sensitivity of the prototype assay was consistently higher than that of the other two assays. It detected 10 of 14 panels two to eight days earlier than the Architect and Elecsys tests.

U.S. and WHO guidelines recommend starting antiretroviral therapy as soon as possible, including immediately after diagnosis of HIV infection. "By being designed to detect HIV infection earlier," Dr. Qiu says, "the prototype assay can play a role in saving critical time for people enrolling in effective antiretroviral therapy."

The prototype assay reduced the second diagnostic window, or trough effect. Several trough bleeds in three of 14 seroconversion panels had between two- and sevenfold higher signal compared with the Architect and Elecsys tests. "The higher signal is driven by enhanced antigen and antibody sensitivity of the prototype," Dr. Qiu said.

The enhanced antigen sensitivity of the prototype assay, she noted, "did not compromise antibody detection."

The assay's antibody sensitivity was tested against the Architect in 543 samples from patients who were at different stages of HIV: acute, symptomatic, and AIDS. The prototype and Architect assays detected 100 percent of the samples, but three of the Architect results showed low reactivity. The sensitivity of low-titer samples was improved two- to 13-fold by the prototype assay over the Architect assay. "The signal-to-cutoff for those three samples is 3.8 to 16," Dr. Qiu said. "But in the prototype, the 3.8 becomes 48.9, and you can see the high signal. This indicates the antibody sensitivity is also improved by the prototype."

The prototype assay maintained broad detection of antibodies against different HIV subtypes. In a study of 473 HIV subtype samples, which included 327 HIV-1 group M samples, 50 HIV-1 group O samples, and 96 HIV-2 samples, the prototype assay detected all samples with a very high signal, Dr. Qiu said.

"In addition, we compared the prototype performance between Architect and Abbott's new Alinity platform, and we found excellent correlation." This comparison involved HIV-1 groups M and O, HIV-1 URF, and HIV-2 samples for antibody detection and, for antigen detection, 52 dilutions of HIV-1 groups M and O and HIV-2 virus isolates.

"From the 473 antibody subtype panels, the slope is 1.1, and the correlation coefficient R2 is .99," she said. "It was similar for the antigen detection. The slope is one, and the R2 is .99 for the results from the 52 diluted HIV virus isolate samples."

The 473 specimens in the HIV genotype panel used in this study were collected and characterized by Abbott's Global Viral Surveillance Program, launched 25 years ago. It has a library of more than 70,000 samples containing

HIV and hepatitis viruses from six continents and 45 countries. “These samples are used to track virus evolution, challenge the performance of Abbott’s tests, and drive continual improvement of testing technology,” Dr. Qiu says.

The prototype assay also demonstrated high specificity. In an evaluation performed on 4,316 fresh blood donors, it demonstrated a specificity of 99.93 percent. When tested on 1,690 specimens from a low-risk population, specificity was 99.76 percent. Of those 1,690 samples, 14 were found to be repeatedly reactive, 10 were confirmed HIV positive, and four were falsely reactive.

In addition, “The signal distributions of both populations were tight,” Dr. Qiu said. “For the blood donor population, the standard deviation to cutoff is 31, and for the low-risk population it is 22. In general, a standard deviation to cutoff greater than 10 is suitable for blood screening, so a standard deviation to cutoff of 31 is considered a very specific assay.”

Another specificity improvement demonstrated by the prototype is reduced heterophilic antibody interference, she said. “There are nine Architect false reactive samples due to heterophilic antibody interference. Some of them had a quite high signal, greater than 400.” All false reactive samples became completely inactive in the prototype. “This shows the improvement.”

The assay will undergo external evaluation by key laboratories. Abbott plans to make it available on the Architect and Alinity platforms.

“This fourth-generation prototype assay is designed to detect highly infectious people who may be missed by existing tests and can play an important role in helping the global community end the HIV epidemic by 2030,” Dr. Qiu says.

Amy Carpenter Aquino is CAP TODAY senior editor.