A single pathway for HIV testing and therapy

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June 2022—By revealing the value of a diagnostic algorithm using quantitative RNA as the second test to confirm reactive HIV screening results, Daniel Gromer, MD, and colleagues say their simulation modeling suggests clinical improvement over the standard-of-care algorithm, and at lower cost if HIV specimen positivity is high.

The current guideline-based standard of care for HIV detection, outlined in CDC recommendations, consists of a fourth-generation HIV p24 antigen/antibody test that, if reactive, is followed by an antibody differentiation immunoassay. If indeterminate or negative, a qualitative RNA test is done (QL-RNA). For therapy, testing starts with a baseline quantitative RNA (QT-RNA) test on a plasma specimen, followed by antiretroviral therapy initiation, and then by serial QT-RNA testing to monitor response.

"Our objective was to use simulation modeling to compare the clinical and cost implications of two HIV diagnostic algorithms," Dr. Gromer says: an RNAplasma algorithm employing QT-RNA as the second test (Ag/Ab→*QT-RNA*→AbDiff) and the standard-of-care algorithm with antibody differentiation as the second test (Ag/Ab→*AbDiff*→QL-RNA).

Simulation studies aren't perfect, admits Dr. Gromer, an infectious disease fellow at Emory University School of Medicine. "All models you use in a simulation setting are kind of a false construct. But you often need to model the truth as closely as you can to tell intrinsic truths about what's actually happening in the world."

Since late 2020, clinicians and laboratories have had the benefit of the FDA's approval of a QT-RNA assay for diagnosis—Hologic's Aptima HIV-1 Quant Dx. On plasma specimens, it's approved for quantitative reporting as a numeric value. On serum specimens, it's approved for reporting as "detectable" or "undetectable."

QT-RNA offered much more, in the view of Dr. Gromer and infectious disease specialists from Yale School of Public Health, Harvard Medical School, and Massachusetts General Hospital. They hypothesized that the QT-RNA test's quantitative results at diagnosis, used as part of a plasma algorithm, could also improve HIV clinical care and reduce costs.

Dr. Gromer

This spring, at the virtual 2022 Advancing HIV, STI and Viral Hepatitis Testing Conference, sponsored by the CDC, Association of Public Health Laboratories, American Sexual Health Association, and American Sexually Transmitted Diseases Association, and in a recent interview, Dr. Gromer explained how the group's study suggests that incorporating the QT-RNA test into the HIV testing algorithm—using it as the second test in place of AbDiff—could lead to faster confirmation of HIV diagnosis, which could expedite antiretroviral initiation and reduce the potential for new transmissions, while also reducing time to reassurance for patients with false-positive antigen/antibody test results.

"There's been somewhat of a disconnect between diagnosis and therapy of HIV, which is one of the major challenges we face in controlling and limiting the spread of HIV," Dr. Gromer tells CAP TODAY. "Diagnosis has a few steps and then therapy initiation has a few steps and there's no single test in the guidelines that acts as a perfect bridge between them." As RNA testing has become much more affordable, faster, and more facile, "I think those

molecular techniques have become more widespread. And there's been enthusiasm for trying to figure out a way of streamlining the HIV testing cascade for diagnosis in particular, and also for screening, that prioritizes RNA testing and deprioritizes antibody differentiation testing."

Both algorithms were examined in a population of specimens tested for HIV, which included specimens with no HIV infection and with HIV infection. For specimens with HIV, they categorized by specific subpopulations: chronic HIV-1, acute HIV-1, elite control of HIV-1, and HIV-2, although the latter two are rare among specimens tested for HIV in the United States.

"We populated the model with data from three large U.S. laboratory systems with low (.25 percent), moderate (.51 percent), and high (1.98 percent) HIV specimen positivity, and we examined the algorithms in each laboratory setting," Dr. Gromer says. Other model input parameters were the tests' performance characteristics, turnaround times (from collection to result reported) based on experience for both reflex (AbDiff, 12 hours; RNA, 24 hours) and return (add 60 hours to reflex test time) testing, and test cost based on the CMS laboratory fee schedule, which lists AbDiff at $13.71, QL-RNA at $35.09, and QT-RNA at $85.10.

The comparison covered two time-based outcomes. The first, time to action, was defined as the time to when clinicians initiate antiretroviral therapy for people diagnosed with HIV or complete the diagnostic algorithm for a specimen without HIV. "This outcome is especially important in some presentations of acute HIV when the antigen/antibody is reactive but the differentiation assay will not be," Dr. Gromer says. The second outcome was time to reassurance, or the time to when clinicians can inform a person with a false-positive antigen/antibody that they have a negative RNA test. Two other outcomes studied were the number of blood draws needed and testing cost.

The base case results when the two algorithms were compared were as follows:

- RNAplasma would reduce time to action compared with the standard of care for persons with HIV from 112 hours to 60 hours.
- RNAplasma would reduce time to reassurance compared with the standard of care for persons with a false-positive Ag/Ab from 132 hours to 60 hours.
- RNAplasma would result in similar costs for all specimens tested: $24.74 per run for RNAplasma versus $24.70 per run for the standard of care.
- RNAplasma would reduce visits for specimen collection before antiretroviral therapy initiation compared with the standard of care for persons with HIV from 2.05 visits/person for the standard of care to 1.01 visits/person for RNAplasma.

In terms of time to action, the only laboratories in which the standard of care is preferred is where antibody differentiation provides results quickly and QT-RNA takes much longer, Dr. Gromer says. For example, standard-of-care testing would result in faster time to action when AbDiff turnaround time is six hours and QT-RNA turnaround time is longer than 76 hours, assuming that ART is not initiated until a specimen for QT-RNA is obtained.

Testing costs would be lower for the RNAplasma algorithm when HIV specimen positivity in the laboratory is higher, the model shows. In low-positivity laboratories, QT-RNA test cost would need to be about $50 for RNAplasma to result in lower testing costs, while at the base cost of $85 per QT-RNA test, RNAplasma would result in lower testing costs if laboratory HIV positivity is high, at .8 percent or greater.

A major thrust of the paper the research team is now working on to report its findings involves how valuable

quantitative results are for monitoring of treatment, for which RNA testing is a Grade A indication. “From personal experience, if someone comes to the emergency room with a fever and they were recently started on therapy for HIV and their viral load is, say, 150 versus 100,000, it makes a huge difference in my understanding of everything that’s going on with that person,” Dr. Gromer says. He hopes that QT-RNA will be incorporated earlier in the diagnostic algorithm. “Because it will, I think, facilitate earlier initiation of antiretroviral therapy if clinicians knew that the quantitative RNA data was available or would be soon available because the test is already in the lab.”

Some laboratories, Dr. Gromer notes, may not have in-house access to the approved QT-RNA assay or other assays, and that may affect on-site or send-out testing decisions as well as specimen handling and shipping requirements (more stringent for RNAplasma). “At least in the academic setting where I worked, the differentiation assay wasn’t available; it became a send-out test and was more like a three-day test than a 30-minute test. Our study needed to take into account that results could take different amounts of time to become available from different laboratories.”

Despite the researchers working in large academic institutions, Dr. Gromer believes they were able to derive findings that apply to different health care settings. “Every different locale is going to have to some extent different workflows, and every local lab or academic lab has its own constraints in terms of labor cost, what the technicians are trained to do and not trained to do on the actual machines, and reagents they have. So our model had to attempt to take into account at least some of these factors and do sensitivity analyses to say, What if this part does take longer, what if this other part is more costly?”

“In general, what we assumed is our base case is a laboratory that has the capacity to do all of these tests, and then we varied each one in terms of turnaround time in the reasonable likelihood that some laboratories will have to send these tests out.”

In answer to a question posed at the HIV diagnostics conference, Dr. Gromer said some laboratories might need to explore different plasma collection time, shipping, and storage conditions to operationalize the use of plasma rather than serum. “Sending a plasma specimen and sending a serum specimen are not the same in terms of processes and actions that happen to them and the shipping and handling,” he notes. “So in order to implement a laboratory testing schema that utilizes plasma would require an upfront decision by a laboratory to systematically obtain plasma specimens for HIV testing, as opposed to using serum, which I think is a little simpler.”

Another attendee raised the question of laboratory expertise and false-positive HIV RNA results.

“Our model did not examine this infrequent occurrence,” Dr. Gromer says. “From my perspective, false-positive RNA results are extremely rare. If I saw somebody with a positive RNA value at 70 copies per mL or 200 copies per mL, I would follow DHHS guidelines regarding retesting. But I wouldn’t want to base my decision-making on an entire algorithm on those small outliers that can be adjudicated afterward.”

Dr. Gromer’s research project had been underway for a while at Massachusetts General Hospital during his medical residency before he moved to Atlanta for his fellowship. Based on his experience with the Atlanta patient population, he has found HIV a challenge to manage. “There are not the ideal sort of funded wraparound services that we would wish to have. And new diagnoses of HIV and complex management of HIV are commonplace.” There are major structural barriers to return visits and repeat specimen draws, and the more these are required, the less likely successful linkage to care becomes.

Given the barriers some populations face, it becomes important to streamline the approach to diagnosis and treatment without breaking the bank, he adds. “That’s one of the reasons we were so excited to take this on and figure out how to eliminate some steps for the average person who is coming for HIV testing.”

For the standard of care to change, Dr. Gromer says, the CDC would likely need to reevaluate the feasibility of implementing the RNAplasma algorithm with major referral labs and potentially partner with some local labs to understand the barriers to implementation and find ways that it could be cost-effective for them.

More than one approved QT-RNA test could simplify change. “Right now, laboratories invested in one company’s machine for its RNAs may ask what do we do with this large, expensive piece of machinery that we have all these expensive reagents for if you want to do an algorithm with a different sort of pathway.” It would be helpful, he says, if the FDA approved quantitative HIV RNA reporting on serum specimens. “There may be a difference in comfort level from laboratory to laboratory as to whether on a serum specimen they feel comfortable reporting a ‘ballpark’ quantitative value, which might provide a huge amount of value to some clinicians” by streamlining the testing cascade and getting people into treatment. Whether there is confidence in that as a reliable number is likely to vary, he says.

“There is a brief but critical disconnect between the diagnostic and therapeutic chains for addressing HIV,” Dr. Gromer says. “Changing technology and approvals of the new QT-RNA assay have allowed us to bridge diagnosis and treatment initiation into a single pathway without sacrificing cost.” While the SARS-CoV-2 pandemic affected the pace of his research team’s modeling study because most of the collaborators were infectious disease and laboratory science professionals inundated with COVID-related work, “I think the pandemic increased our fervor and our hope that this topic will be present in a lot of people’s minds, particularly laboratory and pathology-associated folks.” He is hopeful that the modeling study showing the benefits of the single pathway will lead to a change in practice and potentially an improvement in HIV diagnosis and linkage to care.

Anne Paxton is a writer and attorney in Seattle. Dr. Gromer’s coauthors are Bernard Branson, MD; Paul Sax, MD; Anne Neilan, MD, MPH; Maya Hajny Fernandez; Michael Mina, MD, PhD; David Paltiel, MBA, PhD; and Emily Hyle, MD, MSc.