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Perspective Piece

Rapid HIV Antigen–Antibody Assays and Detection of Acute HIV Infection in Sub-Saharan Africa

Adedotun A. Adetunji,[1]* Moses O. Adewumi,[2] Obaro S. Michael,[3] Samuel A. Fayemiwo,[4] Adesola Ogunniyi,[5] and Babafemi O. Taiwo[6]

[1]*Department of Family Medicine, University College Hospital, Ibadan, Nigeria;* [2]*Department of Virology, College of Medicine, University of Ibadan, Ibadan, Nigeria;* [3]*Department of Clinical Pharmacology and Therapeutics, College of Medicine, University of Ibadan, Ibadan, Nigeria;* [4]*Department of Medical Microbiology and Parasitology, College of Medicine, University of Ibadan, Ibadan, Nigeria;* [5]*Department of Medicine, College of Medicine, University of Ibadan, Ibadan, Nigeria;* [6]*Division of Infectious Diseases, Feinberg School of Medicine, Northwestern University, Chicago, Illinois*

Abstract. Detection of acute HIV infection is a unique problem that fourth-generation HIV assays were expected to alleviate. In this commentary, we draw attention to the limitations and challenges with use of currently available rapid antigen–antibody (Ag/Ab) combination tests for detection of acute HIV infection in sub-Saharan Africa. Laboratory-based HIV-1 Ag/Ab immunoassays are complex, requiring specialized equipment and handling that are currently not affordable in many settings in Africa. The point-of-care Ag/Ab platform on the other hand is easier to deploy and potentially more accessible in resource-limited settings. However, available fourth-generation HIV-1 rapid diagnostic tests have demonstrated poor performance characteristics in field studies where non-B subtypes of HIV-1 dominate. The potential for point-of-care HIV-1 Ag/Ab diagnostics to significantly improve detection of acute HIV infection remains yet to be realized in sub-Saharan Africa. Assay platforms need to be optimized to identify local circulating subtypes, and optimal algorithms need to be determined.

INTRODUCTION

Rapid HIV antibody tests have generally improved access to HIV testing. However, lapses remain in the detection of acute HIV infection, especially in sub-Saharan Africa.[1,2] Acute HIV infection is an early phase of HIV infection (before seroconversion) during which only HIV-1 p24 antigen and/or HIV RNA are detectable in plasma by antigen-based tests. Peak HIV viremia and an absence of distinctive symptoms in some patients make acute HIV infection a period of high infectivity, and the likelihood of HIV transmission has been estimated to be almost 12 times higher per sex act during the period.[3]

The introduction of fourth-generation HIV-1 antigen–antibody (Ag/Ab) detecting diagnostics was hailed as a relevant development to improve detection of acute HIV infection and impact on HIV incidence through interruption of transmission dynamics within sexual networks. This commentary draws attention to the current challenges of using rapid HIV-1 Ag/Ab assays for acute HIV infection detection in sub-Saharan Africa.

DISCUSSION

In sub-Saharan Africa, there is paucity of data on the proportion of testers who receive false-negative HIV results because of testing before seroconversion. Such missed opportunities to diagnose acute HIV infection was highlighted by an African community-based study of care-seeking and of febrile adults who underwent targeted testing with HIV-1 antibody assay and then laboratory-based fourth-generation HIV-1 Ag/Ab assay. According to the study findings, acute HIV infection was diagnosed in five of 506 HIV-1 antibody–negative or discordant patients who met acute HIV risk criteria (prevalence 1.0%, 95% CI 0.3–2.3%).[4]

Fourth-generation HIV tests are available as laboratory immunoassays or point-of-care Ag/Ab tests for detecting HIV-1 p24 antigen as well as HIV-1/2 antibodies. Laboratory-based HIV Ag/Ab tests require highly trained technicians, plasma testing, and complex multistep algorithms to distinguish between p24 antigen and antibody reactivity and to differentiate between HIV-1 and HIV-2 infection.[5,6] Rapid HIV-1/2 Ag/Ab tests which use finger-stick whole blood and differentiate between p24 antigen and antibody results circumvent many of the technical burdens of laboratory-based assays and are attractive to frontline workers in resource-constrained testing programs.[7,8] However, available rapid HIV Ag/Ab assays have demonstrated poor performance characteristics in African field studies where non-B subtypes of HIV-1 dominate.[9–13]

In a Swaziland national survey, the Determine rapid HIV-1/2 Ag/Ab test recorded a sensitivity of zero percent for detecting acute HIV infection, and no advantage was observed over HIV antibody–only assays.[9] In a South African cross-sectional study, the same assay had a sensitivity of 90.7% and a specificity of 100% for detection of HIV-1/2 antibodies, but its sensitivity for detection of p24 antigen was only 10%.[10] Also, a field evaluation of the Determine rapid HIV Ag/Ab assay in Malawi reported that the antibody portion had a sensitivity of 99.4% and a specificity of 99.2%, but the antigen portion (for detecting acute HIV infection) had a sensitivity of zero percent.[11] A report suggests that a CE-Marked HIV Combo Ag/Ab test would have identified 28% of acute HIV infection cases missed by third-generation testing in the VOICE study.[2]

These aforementioned reports and a few others[12,13] give an impression that for now, rapid HIV-1/2 Ag/Ab testing may have only minimal advantage over currently used HIV antibody–only testing in sub-Saharan Africa and cannot reliably substitute laboratory-based HIV Ag/Ab tests in diagnostic algorithms for acute HIV infection. Consistent with this, some regulatory authorities do not recommend using the rapid HIV Ag/Ab assay as the first step in the testing algorithm and advised that all reactive rapid tests should be followed up with a laboratory-based Ag/Ab test.[14] Plausible explanations for the diagnostic shortcomings of some fourth-generation HIV rapid assays include formation of immune complexes between p24

* Address correspondence to Adedotun A. Adetunji, Department of Family Medicine, University College Hospital, 1, Queen Elizabeth Rd., Ibadan 200212, Nigeria. E-mail: adedotun_adetunji@yahoo.com

antigen and HIV antibodies,[15] poor assay sensitivity at p24 antigen plasma levels below specified threshold point,[16] the phenomenon of a second diagnostic window period due to a drop in HIV p24 antigen levels before HIV antibody is detectable,[17,18] and assay-related deficiency in detecting acute HIV infection caused by non-B subtypes of HIV-1.[19] Sub-Saharan Africa shows great HIV-1 diversity with varied subtypes and circulating recombinant forms (mainly subtypes A, C, CRF02_AG, and D) circulating in the region.[20] However, HIV-1 subtype C (predominant subtype in about half of all people living with HIV) and other HIV-1 subtypes have been less investigated or considered in terms of diagnostics when compared with the subtype B.[21] Taken together, available evidence suggests caution in using currently available rapid HIV Ag/Ab assays for detection of acute HIV infection among Africans. Therefore, until more appropriate point-of-care diagnostics for acute HIV infection detection are introduced, laboratory HIV Ag/Ab immunoassay or pooled nucleic acid test may be the dependable approach to detect acute HIV infection among Africans living in settings with high HIV incidence.[22]

CONCLUSION

The potential of rapid HIV Ag/Ab assays to improve acute HIV infection diagnosis has yet to be realized in sub-Saharan Africa. Assay platforms need to be optimized to identify relevant non-B subtypes of HIV-1 because subtype B only may not be a sufficient industry standard for determining HIV test sensitivity and specificity across all populations. Real-world studies of rapid HIV diagnostic testing platforms in Africa are needed to determine optimal algorithms for deploying rapid HIV Ag/Ab assays.

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Authors' addresses: Adedotun A. Adetunji, Department of Family Medicine, University College Hospital, Ibadan, Nigeria, E-mail: adedotun_adetunji@yahoo.com. Moses O. Adewumi, Department of Virology, College of Medicine, University of Ibadan, Ibadan, Nigeria, E-mail: adewumi1@hotmail.com. Obaro S. Michael, Department of Clinical Pharmacology and Therapeutics, College of Medicine, University of Ibadan, Ibadan, Nigeria, E-mail: micobaro@yahoo.com. Samuel A. Fayemiwo, Department of Medical Microbiology and Parasitology, College of Medicine, University of Ibadan, Ibadan, Nigeria, E-mail: dayteet@yahoo.com. Adesola Ogunniyi, Department of Medicine, College of Medicine, University of Ibadan, Ibadan, Nigeria, E-mail: aogunniyi53@yahoo.com. Babafemi O. Taiwo, Division of Infectious Diseases, Feinberg School of Medicine, Northwestern University, Chicago, IL, E-mail: b-taiwo@northwestern.edu.

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