Case report

False reactive HIV-1 diagnostic test results in an individual from Kenya on multiple testing platforms-A case report

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ABSTRACT

Background: Rapid diagnostic tests (RDT) are routinely used in screening for HIV infection. More complex diagnostic algorithms incorporating fourth-generation screening and confirmatory HIV-1/HIV-2 differentiation immunoassays (IA) may be used to confirm HIV infection. Co-infections and autoimmune diseases may lead to falsely reactive HIV diagnostic test results.
Case presentation: A Kenyan man with asymptomatic schistosomiasis and low risk factors for HIV infection demonstrated an inconsistent and discordant pattern of reactivity on HIV RDT, repeated reactivity on fourth-generation IA and positive at a single time-point for HIV-1 on the Geenius HIV1/HIV2 confirmatory assay during the course of a prospective cohort study with HIV repeat testing. The individual initiated antiretroviral therapy following HIV diagnosis. However, his bi-annual behavioral questionnaire suggested low-risk factors for infection. Supplementary confirmatory serologic and nucleic acid tests were performed and gave discordant results. The participant was determined to be HIV uninfected using cell-associated HIV-1 DNA/RNA testing and antiretroviral therapy was discontinued.
Discussion and conclusions: Sole reliance on diagnostic test results may result in misdiagnosis of HIV infection, social harm and potential antiretroviral induced drug toxicity. Interpretation of HIV test results should incorporate multiple parameters.

Introduction

HIV infection is a global public health crisis with over 37 million infected people in 2018 [1]. Kenya has the fourth highest number of HIV-infected people on antiretroviral therapy (ART) in Africa with over one million individuals on treatment at the end of 2018 [1]. Identifying recent HIV infection and early treatment are critical to the success of stemming the HIV pandemic. The increasingly wide-spread use of fourth-generation (4thG) HIV serologic tests, which allow detection of both HIV antigen and antibody, coupled with availability of ART allows earlier identification and treatment of HIV infected individuals and the potential for reducing transmission and improved quality of life [2].

Diagnosis of HIV utilizes a variety of methods ranging from HIV rapid diagnostic tests (RDT) to more complex immunological and molecular tests [3]. WHO recommends a diagnostic algorithm of two sequential tests with different antigen preparations, which if discordant would be resolved with a third assay to exclude but not confirm HIV-1 infection in countries, such as Kenya, with HIV prevalence ($\geq$5 %) [4]. The current Centers for Disease Control and Prevention (CDC) HIV diagnostic algorithm incorporates screening by 4thG immunoassay (IA) for both HIV-1 and HIV-2. Reactive results are followed by testing with a HIV-1/HIV-2 differentiation IA, which if positive for HIV-1 is indicative of laboratory diagnosis of HIV infection [5]. This algorithm allows detection of acute HIV infection, as virus may be detected in the absence of antibody [6].

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We describe the case of an individual enrolled in a prospective study of HIV-1 incidence in Kenya with low risk factors for infection, who had multiple false positive tests on both RDT and 4thG IA over the course of 24 months, resulting in ART therapy for five and a half months.

Case presentation

The case was a 22-year old Kenyan male who enrolled into RV393, an ongoing prospective cohort of HIV-1 incidence and willingness to participate in HIV vaccine trials in Kisumu, Kenya spanning 24 months. The study was approved by the KEMRI Scientific and Ethics Review Unit, Nairobi, Kenya, and Walter Reed Army Institute of Research Institutional Review Board, Silver Spring, MD, USA and conducted in accordance with 32 CFR 219, the United States Department of Defense regulations and all corresponding local regulations and requirements. All participants provided written informed consent. HIV testing was performed at screening, study enrollment (Visit 1) and every three months thereafter using whole blood from finger-stick for RDT and plasma EDTA for IA when necessary. Two RDT were used in the HIV diagnostic algorithm (Fig. 1): Abbott Determine HIV-1/2 Ag/Ab Combo (DET-Ag/Ab; Abbott Diagnostics Medical Co., Matsudo, Japan) and the First Response HIV 1-2-0 (FR; Premier Medical Corporation Ltd., Daman, India). As no tie-breaker was recommended according to the country testing guidelines at the time, in cases of discordant RDT results, the RV393 protocol incorporated laboratory-based 4thG IA testing (GenScreen ULTRA HIV1/2 Ag-Ab, Bio-Rad, Marnes-la-Coquette, France) followed by re-testing in duplicate and an HIV 1/2 discriminatory IA (Geenius HIV 1/2 Confirmatory Assay, Bio-Rad) if at least one of the 4thG IA re-tests was reactive (Fig. 1). Results for the 4thG IA were expressed as the

signal/cut-off (S/CO) ratio to reduce inter-assay variability. A S/CO ratio of ≥ 1 is considered reactive.

A risk-assessment questionnaire including general health, behavioral and sexual risks was administered by the study staff at Visit 1 and every 6 months thereafter. Participants who acquired HIV infection during the course of the study underwent CD4 + T cell count (Alere Technologies, Jena, Germany) and plasma HIV RNA (Abbott M2000rt; Abbott Molecular Diagnostics, Germany) testing at 6-month intervals in addition to other per protocol study-specific procedures. The participant was screened for HIV infection with the DET-Ag/Ab, which was non-reactive and the individual was enrolled into RV393. The individual was again screened for HIV infection 9 days later at Visit 1, and the DET-Ag/Ab RDT was non-reactive (Table 1). Additional testing performed at study enrollment included malaria blood film microscopy and genotyping, hepatitis B surface antigen (HBsAg 3.0 ELISA kit, Bio-Rad Laboratories Inc., Marnes-la-Coquette, France) and hepatitis C antibody (Ortho HCV 3.0 ELISA Test System with Enhanced SAVe, Ortho-Clinical Diagnostics Inc., Raritan, NJ, USA), syphilis (Impact RPR carbon agglutination test kit, Alere Technologies, Orlando, Florida, USA), *Chlamydia trachomatis* and *Neisseria gonorrhea* (Aptima Combo 2 Assay, Hologic Inc., San Diego, CA, USA), hematology, clinical chemistry and CD4 + T cell enumeration. Schistosomiasis testing was also performed at study enrollment on urine using a circulating-cathodic-antigen (CCA) RDT (Rapid Medical Diagnostics, Pretoria, South Africa) and serologically by ELISA (Bilharzia ELISA Test System for IgM and IgG, Diagnostic and Technical Services, Randburg, South Africa). Test results were negative for malaria microscopy and genotyping, hepatitis B and C, *Chlamydia trachomatis*, *Neisseria gonorrhea* and syphilis. The individual was positive for schistosomiasis by the CCA RDT and IgM serology, but negative for IgG antibody. Hemoglobin was 16.4
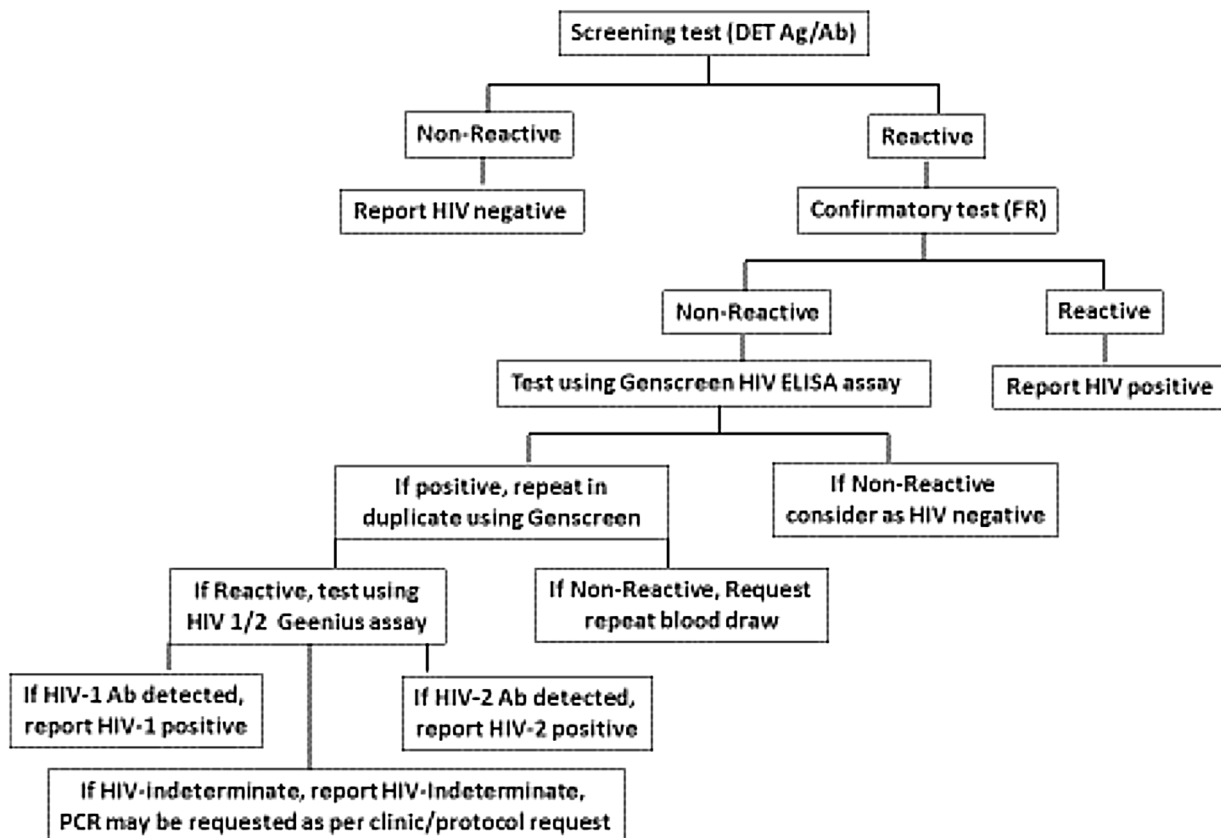

Fig. 1. HIV Testing Algorithm.

Table 1
Summary of HIV Test Results for a study participant enrolled in a study of HIV incidence study in Kisumu, Kenya.

| Study Visit | Time (months) | Rapid Diagnostic Test | | Fourth-Generation HIV 1/2 EIA (Signal/ Cut-Off Ratio) | | HIV1/2 Discriminatory Assay (HIV-1 bands positive) Geenius | HIV-1 proviral DNA | HIV-1 RNA |
		DET- Ag/Ab*	FR	Initial	Repeat (Duplicate Mean)			
1 (Entry)	0	Non-Reactive	Not Done	Not Done	Not Done	Not Done	Not Done	Not Done
2	3.0	Non-Reactive	Not Done	Not Done	Not Done	Not Done	Not Done	Not Done
3	5.4	Reactive	Non-Reactive	Reactive (13.38)	Reactive (13.70)	Indeterminate (gp41)	Not Done	Negative
Follow-up 3	6.5	Not Done	Not Done	Not Done	Not Done	Not Done	Negative	Not Done
4	9.0	Reactive	Non-Reactive	Reactive (5.60)	Reactive (7.19)	Indeterminate (gp41)	Negative	Not Done
Follow-up 4	9.5	Not Done	Not Done	Not Done	Not Done	Not Done	Negative	Not Done
5	12.0	Non-Reactive	Not Done	Not Done	Not Done	Not Done	Not Done	Not Done
6	15.3	Reactive	Non-Reactive	Reactive (8.02)	Reactive (8.72)	Positive (gp41, gp160)	Not Done	Negative
Follow-up 6	16.5	Reactive	Non-Reactive	Not Done	Not Done	Not Done	Positive	Not Done
Visit A	17.6	Not Done	Not Done	Not Done	Not Done	Not Done	Not Done	Negative
Follow-up A**	19.8	Not Done	Not Done	Reactive (>12.41)	Reactive (>12.46)	Negative	Negative	Negative***
9	23.4	Reactive	Non-Reactive	Reactive (5.18)	Reactive (6.04)	Indeterminate (gp41)	Not Done	Not Done

*: DET-Ag/Ab: Abbott Determine HIV-1/2 Ag/Ab Combo; FR: First Response HIV 1-2-0.**: Testing performed at a specialized laboratory.***: Qualitative plasma HIV RNA assay.

g/dL, marginally above the upper limit of the laboratory reference range of 16.1 g/dL [7]. All other hematology, CD4+T cell count (523cells/μL) and clinical chemistry parameters were within the corresponding laboratory reference ranges [7]. The individual reported no history of autoimmune disease or tuberculosis and had never received an influenza vaccination but had received the BCG vaccine during childhood. Three months after the initial visit (Visit 2), the participant was again non-reactive by the DET-Ag/Ab (Table 1) but reported a history of headache seven days prior to this visit. A malaria RDT (Parascreen, Zephyr Biomedical Systems, Tulip diagnostics, Verna, India) was performed in addition to malaria blood film microscopy, both of which were negative.

Approximately 5 months later (Visit 3), the individual returned for his 6-month scheduled protocol visit and was re-tested for HIV infection by DET-Ag/Ab RDT. The test was reactive, but the FR RDT was non-reactive, and the initial and repeat 4thG IA had S/CO ratios >13 (Table 1). Confirmatory testing by the Geenius assay was HIV-1 indeterminate with HIV-specific gp41 antibody only. Malaria blood film microscopy was again negative at this visit. A follow-up dried blood spot (DBS) specimen was collected 1.1 months later (Follow up 3) for HIV proviral DNA testing using Cobas Ampliprep [24] (Roche Diagnostics, Indianapolis, IN, USA), at the Kenyan National Reference Laboratory and was negative. HIV serology test results at nine months (Visit 4) were the same as those at Visit 3, although the S/CO ratio was lower for the 4thG IA (Table 1). A DBS specimen collected two weeks after this visit (Follow up 4) was also negative for HIV proviral DNA.

Twelve months after study enrolment (Visit 5), the DET-Ag/Ab RDT was non-reactive, hence additional testing was not performed. A malaria RDT was also performed at this visit as the participant was experiencing chills, headache, cough and running nose at the time and he reported being treated for malaria two weeks prior to the study visit. On examination, the vital signs were within normal range but had inflammation of throat. Malaria RDT and blood film microscopy were negative and no other tests were done for clinical management; a diagnosis of pharyngitis was made. Schistosomiasis protocol testing by CCA RDT was again positive.

Three months later (Visit 6), the DET-Ag/Ab and FR RDT were reactive and non-reactive, respectively, and the 4thG IA was

reactive (Table 1). Additionally, Geenius testing of the sample was positive for HIV-1 as reactivity was observed to both gp160 and gp41. A follow-up DBS collected about 5 weeks later (Follow up 6) and tested for HIV proviral DNA at the Kenyan National Reference Laboratory was positive. Based on Kenyan national guidelines, the participant was classified as HIV-infected and CD4 + T cell count and HIV viral load measurements were performed. The CD4 result was 654 cells/μL and the viral load result was undetectable. The individual was negative for malaria by blood film microscopy. Sputum and urine were collected for *Mycobacterium tuberculosis* (Cepheid Inc., Sunnyvale, California, USA) and CCA RDT, respectively, and were both negative.

The participant initiated ART (tenofovir, lamivudine and dolutegravir) and Cotrimoxazole (Septrin) within one month of HIV diagnosis according to Kenya national guidelines. The study staff raised concerns about the participant's HIV status based on the risk-assessment questionnaires, inconsistent temporal HIV diagnostic test results and absence of clinical signs of HIV-1 infection. The team requested an additional blood collection (Follow up A) for further evaluation at a specialized HIV testing facility in the United States. Serology testing was performed using 4thG IA (GS HIV Combo Ag/Ab EIA), Genetic Systems HIV-1 Western blot and the Geenius HIV1/2 Supplemental Assay (all from Bio-Rad Laboratories, Redmond, WA, USA). The 4thG IA was again reactive and the Western blot showed a weak antibody band to gp160 only. The Geenius assay was negative for HIV-1 and HIV-2 (Table 1). Qualitative HIV RNA testing was performed on plasma (Aptima HIV-1 RNA Qualitative Assay, Hologic Inc., San Diego, CA). Since the participant was on ART for almost 8 weeks prior to sample collection, it was likely that plasma HIV RNA tests would be negative, hence quantitative cell-associated HIV nucleic acid (both RNA and DNA) was measured using multiple aliquots of whole blood lysates and cell pellets with a modified version of the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test v2.0 (Roche Diagnostics, Indianapolis, IN, USA) [8]. All HIV-1 nucleic acid tests were negative. Based on these results and clinical assessments, the participant was considered HIV uninfected and discontinued ART after a period of 5.5 months. Two years after study enrolment, the participant underwent HIV testing at the RV393 protocol exit visit

(Visit 9) and was reactive for DET-Ag/Ab RDT and 4thG IA, non-reactive by the FR RDT and indeterminate by the Geenius assay (Table 1).

Discussion and conclusions

False positive HIV test results have been attributed to a variety of factors including autoimmune diseases, heterophilic antibody, malignancy, influenza vaccination, malaria and schistosomiasis [9–15]. False reactivity to the Abbott Determine HIV 1/2 (DET-Ab), which detects antibody only, has been widely observed in Africa and Asia [16]. In the present study, the individual showed inconsistent seroreactivity to the DET Ag/Ab RDT, from seroconversion, seroreversion to seroconversion again at a single laboratory over 23.4 months (23.8 months including the screening visit). The DET Ag/Ab RDT has a reported specificity for fingerstick whole blood specimens of 99.8 % (manufacturer's package insert: vers 02732530/R02, August 2013). While the regional specificity of the DET Ag/Ab RDT has not been documented, the DET-Ab RDT has the lowest specificity for African relative to European, North American and Asian plasma/serum samples according to the manufacturer's package insert (vers 241020/R5, August 2013). A study in Tanzania also reported repeated false reactivity of the DET-Ab RDT in participants over a one-year interval [17]. One large international study of the DET-Ab RDT observed that test specificity varied over time at a given site and also within and between countries, which was attributed to multiple factors including polyclonal antibodies including malaria, cross-reacting with HIV antigens [18]. The FR RDT, which has a specificity of 99.5 % (according to the manufacturer's package insert) was consistently non-reactive when incorporated in the algorithm due to reactivity of the DET-Ag/Ab RDT. A comparison of sensitivity and specificity of the DET-Ab and FR RDT in Uganda noted comparable sensitivity, but increased specificity of the FR relative to the DET RDT [19]. Reduced specificity of RDT has been attributed to local infections such as malaria, schistosomiasis, tuberculosis and helminth infection [11]. The Tanzanian study did not observe an association between schistosomiasis and false reactivity with the DET-Ab RDT [17].

The 4thG IA results consistently reflected those of DET-Ag/Ab RDT, and was observed at multiple time points and across two different testing laboratories. False HIV reactivity using 4thG IA has previously been reported for several different commercial 4thG IA [12,14,20–22] and the current study extends this to an additional manufacturer. The 4thG IA used in this study saturates at a S/CO of 12–16 [23], so all values above observed in this study were unequivocally reactive. Fourth-generation IA are desirable in areas with high incidence of HIV infection as they may shorten the time to diagnosis and initiation of ART but several clinical conditions have been associated with false-reactivity, including schistosomiasis, malaria, viral hepatitis, malignancy, and autoimmune diseases [11–13,15]. False reactivity of 4thG HIV diagnostic assays has been linked to cross-reactivity from antibodies resulting from schistosomiasis infection [24] although this association was not found for DET-Ab RDT false reactivity [17].

The Geenius results were also inconsistent, and in one instance confirmed HIV infection due to the presence of HIV-1 gp160 and gp41 antibodies. This may have been due to the HIV gp41 component of the gp160 protein being reactive to non-specific antibody/ies. The finding of weak reactivity to HIV gp160 on the Western blot assay could reflect an increased concentration of multimers of HIV gp41 on this region of the blot relative to monomeric gp41 [25].

The participant referenced in this case study did have an active schistosomiasis infection and this may have resulted in false reactivity to the DET-Ag/Ab RDT, 4thG IA and Geenius assays. A recent case report from Canada documented repeated 4thG IA reactivity (with a different 4thG IA test used in the current study) and confirmation of HIV-1 infection by the Geenius assay three times over a four-month period with reactive bands at HIV Env and Pol antigens in a low-risk individual. The individual had a normal CD4 + T cell count and undetectable HIV-1 viral load but initiated ART based on serologic diagnosis. HIV-1 infection was later ruled out using alternative HIV-1 serologic and nucleic acid tests with ART cessation after 4 months. HIV false-reactivity was attributed to use of anabolic steroids [22]. The participant in RV393 did not report using any form of steroids.

HIV proviral DNA testing further supported HIV-1 diagnosis by serology and subsequent ART initiation for the participant. The Kenyan testing laboratory serves as a national HIV confirmatory facility, therefore most referred specimens would be from HIV-infected individuals. It is possible that there was a specimen mix-up or PCR contamination at the laboratory as an additional battery of HIV nucleic acid testing at a specialized laboratory failed to confirm the result.

In summary, depending on the timing of the participant's study visit, the use of the CDC recommended algorithm for HIV diagnosis could have led to misdiagnosis of HIV infection, and consequently, potential social harm and drug toxicity. HIV infection was ruled out due to the study team's concern about the low risk factors of the individual, which resulted in additional specimen collections and supplemental HIV diagnostic tests. This report highlights the importance of repeat serologic testing and the use of supplemental assays in the diagnosis of HIV infection. Additionally, HIV diagnostic test results should be considered in the context of individual and regional risk factors.

Consent

Written informed consent for publication was obtained from the participant.

Authors' contributions

Conceived and designed the experiment: CP
Performed the experiment: VS, JO, JDO, ER, JKO, LO
Analyzed the data: MS
Wrote the paper: JO, MS
Reviewed the manuscript: MS, LO, VS, JKO, MI, CN, LA, EK, TC, CP

Ethics approval and consent to participate

Ethical approval for the study was obtained from KEMRI Scientific and Ethics Review Unit, Nairobi, Kenya, and Walter Reed Army Institute of Research Institutional Review Board, Silver Spring, MD, USA. Written informed consent was obtained from each participant prior to enrollment.

Availability for data and materials

All data generated or analyzed during this study are included in this published article

Disclaimer

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. The investigators have adhered to the policies for protection of human subjects as prescribed in AR 70–25.

Declaration of Competing Interest

The authors report no declarations of interest.

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