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HIV misdiagnosis: A root cause analysis leading to improvements in HIV diagnosis and patient care

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ABSTRACT

Background: Standard diagnostic testing for HIV infection has traditionally relied on a high sensitivity HIV antibody screening test using an enzyme-linked immunosorbent assay (ELISA) followed by a high specificity antibody confirmatory test such as a Western Blot. Recently several of the screening assays have been enhanced with an ability to identify p24 antigen thereby narrowing the diagnostic window.
Objectives: To explore the implications of enhanced HIV screening methods that may be leading to HIV misdiagnoses.
Study design: A patient deemed to be an HIV infected 'elite controller' was found to be misdiagnosed when undergoing detailed investigations prior to initiating antiretroviral therapy. A root cause analysis was performed to identify the causative factors of this misdiagnosis. A retrospective review of all "elite controllers" in Alberta, Canada revealed challenges of current HIV testing algorithms.
Results: Technical and human factors were identified as being causative in this HIV misdiagnosis including (i) high rates of false reactive results on the Abbott ARCHITECT HIV-1 & 2 COMBO EIA, (ii) human error in reading the initial Western blot, (iii) HIV algorithmic directives in which confirmatory (Western blot) testing was not performed on a repeatedly reactive screen test. The outcome of this analysis identified opportunities for improvement, including implementation of a newly approved (automated) confirmatory assay and improved communication between the clinician and laboratory.
Conclusions: HIV testing remains problematic despite significant advances in HIV test performance and algorithm development, presenting new and unexpected issues. Ensuring a high-quality management system including implementation of the latest HIV technologies and algorithms along with human resources and policies are required to minimize the impact of false positive diagnoses, especially in the era of universal screening and 'test and treat' recommendations.

1. Background

Since 1985, the cornerstone for the diagnosis of human immunodeficiency virus (HIV) infection has been the detection of antibodies against HIV. The standard diagnostic algorithm has consisted of a high sensitivity screening test for antibodies to HIV using an enzyme-linked immunosorbent assay (ELISA) followed by a high specificity confirmatory test, which often has been a Western Blot (WB) [1,2]. The reason for this two-stage testing format is due to the low positive predictive value (PPV) observed in screening tests when used in low-prevalence populations despite the exquisite sensitivity and specificity reported in the latest generation enzyme immunoassays (EIAs). The resulting increase in false reactivity at the screening phase necessitates the need for confirmatory testing (e.g. WB) [1,2].

In 2014, the guidelines for HIV testing were published by the Centers for Disease Control (CDC) to include a fourth generation antibody/antigen EIA followed by an HIV-1/HIV-2 antibody differentiation assay and molecular test (where necessary) to resolve HIV diagnosis [1]. This new algorithm took into consideration the latest generation technologies and represents the most advanced approach to closing the

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Table 1
Diagnostic test results on Index Case.

			Sample ID/Collection date/Result source				
			Sample 1 Apr 25/13	Sample 2 May 30/13	Sample 3 Dec 3/14	Sample 4 Feb 24/15	Sample 5 Apr 21/15
Type	Location	Assay					
Serological	Prov Lab	HIV Serology Abbott ARCHITECT	19.66 (cutoff:1.00)	17.53 (cutoff:1.00)			26.64 (cutoff:1.00)
	Cgy	HIV AG/Ab Combo EIA	Reactive	Reactive			Reactive
	Prov Lab Edm	HIV Serology Abbott ARCHITECT HIV AG/Ab Combo EIA	Reactive (~20)	Reactive (~20)		22.16 (cutoff:1.00) REACTIVE	Reactive
	Prov Lab Edm	GS HIV-1 Western Blot confirmatory Test original	POSITIVE	Negative (test Feb 26/15)		Negative	Negative
	Prov Lab Edm	GS HIV-1 Western Blot Confirmatory Test repeat	Negative (test Feb 26/15)				
	SDCL	Siemens Centaur HIV Ag/Ab Combo assay				Non-Reactive	Non-Reactive
	NLHRS Serology				Negative	Negative	Negative
Molecular	NLHRS Molecular					Negative	Negative
Molecular (quant)	NLHRS	Roche COBAS® AmpliPrep/ COBAS®TaqMan® HIV-1 Test v2.0			Target Not Detected		
	Prov Lab	Abbott Real Time HIV-1					Not Detected
	CLS	Abbott Real Time HIV-1				< 40 copies/mL	< 40 copies/mL
	CLS	Abbott Real Time HIV-1	Viral load tests also all " < 40 copies/mL" for samples collected: May 10/13, Aug 7/13, Oct 30/13, Feb 19/14, Nov 26/14				

HIV window period from time of exposure [1]. Furthermore the CDC has previously recommended the expansion of HIV testing from high-risk individuals to universal screening for adults (13–64 years age) in health care settings [3]. Considering these significant advances in testing performance and algorithm development, a concern regarding an increase in false-positive HIV diagnoses in low-risk populations has emerged [4].

Recent research and patient care guidelines, advocating for widespread HIV testing and the earlier use of antiretroviral therapy (ART), have placed pressure on the HIV diagnostic algorithm and exacerbated the possibility and consequences of an incorrect HIV diagnoses. These include drug treatment toxicity and increased costs to the healthcare system in addition to the already significant personal and social implications of a false-positive diagnosis [5–7].

In this report, we describe a case of a misdiagnosis of HIV. This error prompted a root cause analysis, leading to identification of causative factors resulting in implementation of new procedural and policy changes including a new HIV-1 & 2 antibody differentiation assay. Furthermore, a detailed review of five patients identified in the root cause analysis with atypical HIV testing results highlighted the emerging challenges for the laboratory in accurate diagnosis of HIV, particularly soon after infection.

2. Objectives

To explore the implications of enhanced HIV screening methods that may be leading to HIV misdiagnoses. To identify opportunities for improving and refining our ability to diagnose and rapidly enroll HIV-positive individuals into care and treatment.

3. Study design

3.1. Diagnostic testing

(a.) Alberta Provincial Laboratory of Public Health (APLPH): All HIV diagnostic testing in Alberta is undertaken by the APLPH (Edmonton). All HIV care in southern Alberta is provided by the S Alberta HIV Clinic (Calgary) (SAC) [8]. At the time of testing APLPH used a standard testing algorithm beginning with the Abbott ARCHITECT (Architect) HIV Ag/Ab Combo EIA (Abbott, Chicago, Illinois, USA) in the screening phase followed by the WB (Genetic Systems HIV-1 Western blot, Bio-Rad Laboratories, Redmond, WA, USA). During the time of our root cause analysis the recently approved (Canada) Bio-Rad Geenius HIV ½ antibody diagnosis and differentiation assay was also implemented [9]. The Abbott HIV-1 RealTime Viral Load assay (Abbott, Chicago, Illinois, USA) is used for patient management.

(b.) The National Laboratory for HIV Reference Services (NLHRS): The NLHRS is a national reference laboratory for Canadian public health laboratories. It is an ISO 15189 accredited laboratory and utilizes a combination of commercial and in-house testing methods. The NLHRS-serology algorithm includes the bioLytical INSTI HIV-1/HIV-2 rapid antibody, Bio-Rad HIV-1 p24 antigen, Innogenetics Inno-Lia HIV-1/2 Score, in-house radioimmunoprecipitation (RIPA) and the Bio-Rad Geenius HIV 1 & 2 test. The NLHRS-molecular algorithm includes the Roche Cobas Ampliprep/Cobas Taqman HIV-1 v2.0, Roche COBAS CAP/CTM HIV-1 *Qual*, Abbott HIV-1 RealTime Viral Load assays. It also utilizes a comprehensive set of in-house PCRs to diagnose and differentiate HIV-1 and HIV-2 targeting the LTR, *gag*, *pol* (integrase) and *env* (gp41). The NLHRS also participates in several domestic and international proficiency testing programs.

(c.) Saskatchewan Disease Control Laboratory: The Advia Centaur HIV Ag/Ab Combo EIA assay was used during our root cause analysis, to help confirm false-reactivity in the Abbott Architect HIVAb/Ag EIA used by APLPH.

4. Results

4.1. Index case

An asymptomatic 23-year-old man with minimal HIV risk (unprotected heterosexual sex in a low prevalence area) underwent routine HIV testing at APLPH. Fourth generation screening EIA (ARCHITECT) was reactive (S/co 19–22), and was confirmed by WB as HIV-1 positive (Table 1). The first HIV positive result triggered clinical follow-up and linkage to HIV care. Repeat serological screening two weeks later was again reactive, and WB was not repeated (in accordance with existing laboratory HIV diagnostic algorithm). Over the next year and a half in the absence of ART the patient's CD4 counts remained within normal range and plasma RNA viral loads were undetectable. The patient was therefore being followed as a potential 'elite controller" [10–12]. At 18 months post serological diagnosis, a sample was referred to the NLHRS to establish a baseline proviral DNA level prior to ART. A negative