False negative syphilis enzyme immunoassay results in two HIV-infected case-patients

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Background:

Routine syphilis screening is currently recommended for high risk individuals, including HIV-infected persons and men who have sex with men (MSM). The CDC recommends syphilis screening with a nontreponemal test followed by a confirmatory, more specific, treponemal test. However, widely available automated enzyme immunoassays (EIAs) have led many laboratories to adopt a "reverse sequence" syphilis screening (RSSS) algorithm. With RSSS, the sera is initially tested with a treponemal EIA and followed by a quantitative nontreponemal test if the EIA test is reactive. As treponemal antibodies appear earlier, RSSS should have greater sensitivity in addition to greater specificity. We present two case reports involving HIV-infected MSM highlighting potential problems with the RSSS approach.

Case Reports:

Case 1: 37 y/o HIV-infected MSM seen by his primary care physician (PCP) on 9/24/15 with rash suggestive of 2^0 syphilis. Serological tests for syphilis (STS) revealed: reactive RPR, reactive VDRL (1:32), nonreactive EIA. Patient diagnosed and treated for "fungal" skin infection. Follow-up visit 10/1/15: no improvement in rash; repeat STS: unchanged. Patient referred to Hawaii Department of Health (HDOH). He was seen and treated on 10/16/15 with 2.4 mU penicillin G IM and rash resolved. Follow-up STS obtained 12/26/15 revealed: 4-fold titer decrease in VDRL, but EIA nonreactive. Serum aliquot from 12/26 sent to CDC reference lab. STS demonstrated reactive RPR (titer 1:16), EIA still nonreactive, but reactive TP-PA.

Case 2: 20 y/o asymptomatic HIV-infected MSM, recent contact (w/i 1 month) to 1^0 syphilis. Seen by neighbor island HDOH District Health Office on 11/9/15. STS revealed: reactive RPR, reactive VDRL (titer 1:1), nonreactive EIA. Patient referred to PCP for evaluation and treatment. Repeat STS drawn by PCP 2 days later showed nonreactive RPR. Patient not treated. Patient returned to PCP 1/7/16 with rash suggestive of 2^0 syphilis, plus history of penile lesion 1 week after initial office visit. STS revealed: reactive RPR, reactive VDRL (1:128), and reactive EIA.

Discussion:

Case 1 provides clear evidence of a false-negative EIA test result while Case 2 appears (by history) to demonstrate possible delayed identification of treponemal antibodies with the EIA. Most reports of unusual serologic responses in HIV-infected patients have been of biological false positive nontreponemal test results, however, reports of false negative nontreponemal and treponemal test results have also been documented. An earlier study suggested that false negative treponemal test results in the setting of HIV infection should be suspected when nontreponemal tests are reactive at higher titers (i.e., ≥1:8). Case 1 presented in such a manner. While treponemal tests are considered to be more specific and sensitive that nontreponemal tests, two recent studies have noted the Trep-Sure EIA to be less sensitive than the RPR or VDRL. The TP-PA test is currently considered the most valid (sensitive and specific) confirmatory treponemal test and can be used to resolve discordant test results. The CDC has noted that ". . . if sera is TP-PA nonreactive, syphilis is unlikely." While treponemal tests are widely considered more sensitive and specific than nontreponemal tests, one must keep a high index of suspicion for syphilis especially in HIV-infected case-patients.

Table 1: Summary of data from 2 HIV-infected case-patients with false-negative syphilis treponemal enzyme immunoassay results, Honolulu, HI, 2015

Case-patient 1	9/24/2015: Primary care physician office visit	10/1/2015: Primary care physician office visit	12/26/2015: Follow-up (post-treatment)* Hawaii Department of Health STD Clinic
	Hawaii State Laboratory	Hawaii State Laboratory	Hawaii State Laboratory
	Qualitative RPR: reactive	Qualitative RPR: reactive	Qualitative RPR: reactive
	Quantitative VDRL: reactive 1:32	Quantitative VDRL: reactive 1:32	Quantitative VDRL: reactive 1:8
	EIA: nonreactive	EIA: nonreactive	EIA: nonreactive
	Relevant physical examination: desquamating rash: palms, feet		
			Centers for Disease Control and Prevention Reference Laboratory
			Quantitative RPR: reactive 1:16
			TP-PA: reactive
			EIA: nonreactive
Case-patient 2	11/9/2015: Initial visit to Hawaii Department of Health District Health Office	11/11/2015: Initial primary care physician office visit	1/7/2016: Follow-up primary care physician office visit**
	Hawaii State Laboratory	Commercial Laboratory	Hawaii State Laboratory
	Qualitative RPR: reactive	Qualitative RPR: nonreactive	Qualitative RPR: reactive
	Quantitative VDRL: reactive 1:1		Quantitative VDRL: reactive 1:128
	EIA: nonreactive		EIA: reactive
	Relevant history: recent contact to primary syphilis		Relevant history: developed penile lesion mid-November; relevant physical exam: maculopapular rash: palms, and feet

*10/16/2015: Case-patient 1 treated by Hawaii Department of Health with 2.4 mU benzathine Penicillin G IM

**1/7/2016: Case-patient 2 treated by primary care physician with 2.4 mU benzathine Penicillin G IM

Abbreviations: RPR=rapid plasma reagin; VDRL=Venereal Disease Research Laboratory; EIA=enzyme immunoassay