

Aerospace Medicine Clinic

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You are seeing a 21-yr-old air traffic controller who is taking 50 mg bicittegravir, 200 mg emtricitabine, and 25 mg tenofovir for a diagnosis of human immunodeficiency virus (HIV). He presented to an urgent care facility 16 mo ago with full-body rash, fever, body aches, enlarged lymph nodes, and lesions on his genitals. His initial screening for HIV was positive as were labs for herpes and syphilis. He was treated for early syphilis with a one-time dose of 2.4 million units of penicillin G with appropriate response of his rapid plasma reagin (RPR) titers from 1:32 to 1:2. The Centers for Disease Control and Prevention (CDC) recommends this dosing and treatment for primary and secondary syphilis regardless of HIV status.⁶ Confirmatory HIV testing returned positive the following week. He was evaluated by an infectious disease specialist, who determined he was stage 1 by CDC criteria with a CD4 of $723 \text{ cells} \cdot \mu\text{L}^{-1}$ and viral load of $38,243 \text{ copies} \cdot \text{mL}^{-1}$.² Labs drawn 2 mo after initiating antiretrovirals showed a viral load of $30 \text{ copies} \cdot \text{mL}^{-1}$, CD4 of $648 \text{ cells} \cdot \mu\text{L}^{-1}$, and RPR titers of 1:32. His HIV viral load has been undetectable on testing every 3 mo since that time and he has had no other syphilis testing. He has no history of acquired immunodeficiency syndrome-defining illnesses, no longer engages in high-risk sexual activities, denies any illnesses since initiating antiretroviral therapy, and has taken no antibiotics since his initial diagnosis. Positive findings on physical examination include diffuse hyperreflexia of the upper and lower extremities, slightly decreased proprioception of the left great toe, and several beats of clonus at each ankle.

1. What is the most concerning finding on review of his history?
 - A. His CD4 count decreased from 723 to 648 cells $\cdot \mu\text{L}^{-1}$.
 - B. Enlarged lymph nodes were observed on initial presentation.
 - C. Secondary syphilis should be treated with 2 wk of antibiotic therapy.
 - D. RPR titers went from 1:2 to 1:32 on repeat testing and he has taken no antibiotics.
 - E. The infectious disease specialist placed him in HIV infection stage 1 by CDC criteria.

ANSWER/DISCUSSION

1. D. The patient's RPR titers showed appropriate response from 1:32 to 1:2 after he was treated for what was believed to be early syphilis 16 mo ago. However, the follow-up labs 2 mo after treatment showed a return to 1:32, which indicates reinfection or treatment failure. He reports no history of further treatment or new illnesses/symptoms. Therefore, he likely now has late latent syphilis. It is also concerning that he has neurological findings on clinical examination. His CD4 count did decrease slightly, but it remained greater than $500 \text{ cells} \cdot \mu\text{L}^{-1}$, which continues to meet HIV infection stage 1 by CDC criteria.

Your concerns prompt consultation with an infectious disease specialist, who agrees with your assessment. The CDC recommends a single intramuscular dose of 2.4 million units of benzathine penicillin G for those with early latent syphilis, but three intramuscular doses of 2.4 million units of benzathine penicillin G given at 1-wk intervals for those with late latent syphilis.⁶ As this individual's titers reverted more than 12 mo ago, this represents late latent syphilis.³ While the patient denies any recent illnesses, memory issues, or motor/sensory dysfunction, the specialist also concurs that the neurological findings on examination raise suspicions for neurosyphilis in the setting of treatment failure. Due to these concerns, the specialist recommends a lumbar puncture to assess for evidence of *Treponema* in the cerebrospinal fluid. The patient undergoes lumbar puncture, and the cerebrospinal fluid shows no evidence of infection. Therefore, you begin a workup for hyperreflexia and all labs return within normal limits, except for a low-normal vitamin B12. You decide to obtain magnetic resonance imaging of the spine but must determine the most likely location for a lesion to appropriately target the imaging.

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2. If a spinal cord lesion were causing this individual's neurological findings, where would you expect the lesion to be located?
- C3-4.
 - T3-4.
 - T6-9.
 - T12-L1.
 - L5-S1.

ANSWER/DISCUSSION

2. **A.** Diffuse hyperreflexia in the upper and lower extremities indicates a lesion above the level of the hyperreflexia. As the individual had hyperreflexia to the bilateral upper and lower extremities, C3-4 is the most likely of the above choices in this individual. While clonus was only noted in the lower extremities, other commonly tested clonus reflexes include masseter, patellar, biceps, and triceps.¹³ Ultimately, the patient was found to have a syrinx located at C3 on magnetic resonance imaging that was thought to be too small to cause his symptoms. It was also not thought to be secondary to his diagnosis of HIV or late latent syphilis. Interestingly, his hyperreflexia and clonus resolved after treatment of late latent syphilis, raising the possibility that his hyperreflexia was, in fact, a subtle sign of neurosyphilis. However, it is also possible that the hyperreflexia was due to increased sympathetic tone, as he was nervous on initial examination, day-to-day variation in this individual, or another cause. You recommend that the patient begin taking vitamin B12 supplementation and follow up with his primary care manager. Given the individual's concerns for the return of his syphilis diagnosis, he asks if there is a testing schedule that he should follow to ensure his current course of antibiotics effectively treated his diagnosis of late latent syphilis.

3. Given the patient's history, what is the most appropriate schedule to perform monitoring for response to treatment for late latent syphilis?
- 3, 6, 9, 12, and 24 mo.
 - 6, 12, and 24 mo.
 - 3, 12, and 24 mo.
 - 6, 18, and 36 mo.
 - 6 and 12 mo.

ANSWER/DISCUSSION

3. **B.** The schedule for monitoring treatment response for late latent syphilis with a quantitative nontreponemal serologic test is the same for both HIV-positive and HIV-negative individuals: 6, 12, and 24 mo.⁴ In HIV-positive individuals with primary or secondary syphilis, the schedule for assessing treatment response is 3, 6, 9, 12, and 24 mo.⁶ Individuals diagnosed with primary or secondary syphilis who have no history of HIV should undergo serologic testing at 6 and 12 mo.⁵ Now that his late latent syphilis has been managed, you can begin to discuss

the aeromedical risks of HIV with him, which include development of progressive immunodeficiency, neurocognitive dysfunction, and adverse effects related to his antiretroviral therapy. You explain that progressive immunodeficiency is unlikely if he maintains excellent medication adherence and that current regimens do not have the same profile of significant side effects that older antiretroviral medications had. However, you inform him that HIV-associated neurocognitive disorder (HAND) has been reported in individuals who have no detectable viral load and are otherwise healthy. Overall incidence of HAND in several large studies ranges from 14–52%.¹ Cognitive changes associated with HAND could include executive dysfunction, memory impairment, and loss of impulse control. More subtle impairments could include compromise in cognition, motor function, and behavior.

4. How frequently would the Federal Aviation Administration (FAA) require him to undergo neuropsychological testing to ensure that he has no detectable neurocognitive declines?
- Every 3 mo.
 - Every 6 mo.
 - Every 12 mo.
 - Every 24 mo.
 - Every 36 mo.

ANSWER/DISCUSSION

4. **C.** First- and second-class airmen with HIV require neuropsychological evaluation annually, whereas third-class airmen require testing every other year.⁸ After educating him on the FAA timelines, he asks if there is anything he can do to prevent progression to HAND. He states that both parents have a history of diabetes. His father has a history of alcohol abuse and his mother has a history of hypertension and hepatitis C. He states that he will strictly adhere to his medication regimen, maintain a monogamous relationship with his fiancé, and always wear condoms. You inform him that while he could progress to HAND unexpectedly, there are several factors that increase the risk.

5. Of the diagnoses in his family history, which of the following increases the risk of HAND?
- Diabetes.
 - Hypertension.
 - Hepatitis C.
 - Substance abuse disorders.
 - All of the above.

ANSWER/DISCUSSION

5. **E.** Medical comorbidities, coinfection, substance abuse disorders, psychopathology, and socioeconomic factors have been tied to the development of HAND in medical literature.¹² The patient's age makes it difficult to determine the likelihood to

progress to HAND, as the CHARTER and POPPY studies had an average age of 40–50 yr.^{7,9} Also, individuals in these studies had to take antiretroviral medications that had more significant side-effect profiles than those that are presently used for treatment. The aeromedical concerns in this individual regarding HAND are subtle decrements that are imperceptible to him or others that could cause lack of attention to detail or inability to multitask.

None of the military branches recommend waivers for untrained assets. The Army considers waivers on a case-by-case basis for initial applicants for classes 2, 3, and 4 and all classes for trained individuals*; the Air Force considers waivers for flying classes II and III, Air Traffic Control, Ground Based Operators, and Special Warfare¹⁰; and the Navy considers waivers on a case-by-case basis for classes II, III, and IV.¹¹ Aviation Medical Examiners must defer to the FAA.⁸ All military branches and the FAA require neuropsychological testing to be performed prior to waiver consideration.

The individual's syphilis was treated to resolution with no recurrence and no neurological sequelae. He continues to practice safe sex with strict adherence to condom use and his viral load is currently undetectable. He strictly adheres to his medication regimen and will be followed at regular intervals to ensure no subtle neurocognitive deficits.

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*U.S. Army Aeromedical Activity. Human immunodeficiency virus (HIV) infection. In: Aeromedical policy letters and aeromedical technical bulletins. Ft. Rucker (AL): U.S. Army Aeromedical Activity; 2021:85. [Accessed April 5, 2022]. Available from <https://aero.health.mil/> to those with access.

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