A 45-year-old immunodeficiency virus (HIV)-positive man presents with a two-month history of numbness in both feet. Examination reveals bilateral loss of light touch to mid-calf, reduced vibration sense at the ankle and absent ankle jerks. His CD4 positive (CD4+) T cell count is 250 cells/µL and HIV viral load is 5000 copies/ml. His current anti-retroviral (ARV) drug therapy is stavudine (D4T), lamivudine (3TC) and nevirapine.

The most likely diagnosis is

A. Guillain-Barré syndrome
B. HIV-induced neuropathy
C. cytoegalovirus (CMV) neuropathy
D. ARV-induced neuropathy
E. vitamin B12 deficiency

There are a number of distinctive neuropathic syndromes, which can be classified according to the timing of their appearance during HIV infection, their etiology, and whether they are primarily axonal or demyelinating. The most common of these is peripheral neuropathy, also referred to as distal symmetric peripheral neuropathy.

**EPIDEMIOLOGY —**
- prevalence 9 to 63 percent, variability reflects differences in the degree of immunosuppression (higher prevalence with more advanced disease), in the definition of the neuropathy (symptomatic or asymptomatic), and in exposure to neurotoxic antiretrovirals

**Risk factors**
- advanced immunosuppression
- the level of HIV viremia also correlated increased 2.3-fold in patients with an HIV RNA level >10,000 copies/mL
- aging,
- additional medical problems such as diabetes,
- the nadir CD4 count,
- nutritional deficiencies,
- mitochondrial polymorphisms
- toxicities of dideoxynucleosides - the use of didanosine, stavudine, and nevirapine. The combination of didanosine, stavudine, and hydroxyurea was particularly neurotoxic; this combination is no longer used as antiretroviral treatment.

**Effect of HAART on natural history —** In most studies, the incidence of HIV-associated DSPN appears to have decreased compared to pre-HAART cohorts, suggesting that effective suppression of HIV itself may have a beneficial effect on peripheral nerve function

**PATHOGENESIS —**
- multifactorial.
- DSPN is termed a “dying-back” neuropathy to reflect the pattern of distal fiber loss. It involves myelinated and unmyelinated axons of all sizes; this pattern of axon loss is indistinguishable from that seen with other toxic neuropathies.
- HIV itself may lead to local axonal injury through two separate mechanisms
  - indirect route is via neuronal apoptosis
  - direct, local toxicity mediated through activation of mitochondrial caspases.

Many patients with HIV are also coinfected with hepatitis C, which is also associated with peripheral neuropathy [32]. It is unknown as to whether there are additive or synergistic effects of these two viruses on peripheral nerve function.

**Role of drugs**
- Many cases of distal symmetrical polyneuropathy are iatrogenic, due to intrinsic neuronal toxicities of certain antiretroviral medications
The neuropathy is indistinguishable electrophysiologically from HIV-associated DSPN, although the hands may be affected more often in drug-induced cases. The incidence of neuropathy is dose-dependent and increases with the duration of drug exposure. The onset is typically seven to nine weeks after beginning therapy. The incidence of drug-related neuropathy correlates directly with the degree of mitochondrial toxicity of particular nucleoside reverse transcriptase inhibitors, although a direct link between toxicity and oxidant stress has not been demonstrated. Commonly implicated agents include stavudine (d4T) and to a lesser extent didanosine (ddI). The greatest risk was seen with the use of zalcitabine (ddC), which is rarely used by clinicians today. The potential neurotoxicity of antiretroviral drugs does not preclude their use, since the beneficial effects on viral load suppression and immune function recovery appears to outweigh their potential neurotoxicity.

Other medications
- Vincristine, which may be used to treat Kaposi's sarcoma
- Dapsone, which may be used to treat or prevent Pneumocystis jiroveci (formerly carinii) pneumonia
- Thalidomide, which may be used to treat aphthous ulcers
- Isoniazid and ethambutol, which are used to treat tuberculosis
- Nevirapine, a non-nucleoside reverse transcriptase inhibitor, used to treat HIV infection.

CLINICAL MANIFESTATIONS
- Usually manifests as bilateral tingling, and numbness in the toes. The neuropathy gradually spreads proximally in the lower extremities, with only rare involvement of the upper extremities.
- The spread of sensory symptoms usually occurs over weeks to months. Neuropathic pain is common and may be the presenting symptoms.
- Neurologic examination shows
  - Sensory loss to all sensory modalities (vibration, pinprick, temperature) in a stocking distribution,
  - Deep tendon reflexes are reduced or absent at the ankles and occasionally at the knees in more severe cases.
  - Distal weakness in the lower extremities can occur, although most patients have only sensory symptoms and signs.
  - Sensory findings in the hands are more commonly associated with drug toxicity. HIV-related DSPN may evolve from painful to painless numbness.
  - The presence of brisk knee reflexes in patients with sensory loss raises the possibility of coexistent myelopathy,
  - While the presence of proximal weakness or diffuse areflexia should prompt consideration of acquired inflammatory demyelinating polyradiculoneuropathy, such as Guillain-Barre syndrome.

DIAGNOSIS — The diagnosis of peripheral neuropathy syndromes in HIV-infected patients is based mainly upon the clinical picture and physical examination.

Features that would prompt further evaluation, such as electromyography (EMG) and nerve conduction studies (NCS), may include significant weakness or asymmetry of signs. These findings may raise the possibility of alternative diagnoses (eg, acquired demyelinating polyradiculoneuropathy or vasculitic neuropathy).

Laboratory testing — The evaluation of distal symmetrical polyneuropathy should include blood work to screen for other causes of this type of neuropathy. A typical panel would include: Hepatitis C antibody Vitamin B12 and folate levels Thyroid stimulating hormone assay Blood glucose Blood urea nitrogen and creatinine Serum protein electrophoresis and immunoelectrophoresis RPR

Although these laboratory tests are considered routine in the evaluation of DSPN, they are usually unremarkable in HIV-related or drug-induced polyneuropathy.

TREATMENT — Treatment options for HIV-related and drug-induced distal symmetrical polyneuropathy are limited.

- HAART
If potentially neurotoxic drug is being used, such as stavudine (d4T), or didanosine (ddI), or thalidomide, it should be discontinued whenever possible.

Symptomatic approach — The classes of drugs used include anticonvulsants, tricyclic antidepressants, topical analgesics, anti-inflammatories, and opioids for recalcitrant symptoms.

Guillain-Barré syndrome

Cardinal clinical features of Guillain-Barré syndrome (GBS) are
- progressive, fairly symmetric muscle weakness
- accompanied by absent or depressed deep tendon reflexes.
- Patients usually present a few days to a week after onset of symptoms.
- The weakness can vary from mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory, and bulbar muscles.

Unusual features of GBS include papilledema, facial myokymia, hearing loss, meningeal signs, vocal cord paralysis, and mental status changes.

GBS usually progresses over a period of about two weeks. By four weeks after the initial symptoms, 90 percent of GBS patients have reached the nadir of the disease. Disease progression for more than eight weeks is consistent with the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

cytogevalovirus (CMV) neuropathy

Neurologic manifestations — CMV infection has been associated with numerous neurologic sequelae in the immunocompetent host.

Encephalitis — Although rare, encephalitis is a serious potential complication of CMV infection and this entity should be considered in the differential diagnosis of unexplained encephalitis.

Guillain-Barré syndrome — Guillain-Barré syndrome (GBS) has been associated with a variety of infectious agents, including Campylobacter and CMV. Patients with CMV-related GBS are generally younger and experience more prominent sensory deficits, respiratory insufficiency, and cranial nerve impairments than those with Campylobacter-related and idiopathic forms of the syndrome. Recovery from GBS also appears to be slower in patients in whom either CMV or Campylobacter infections are identified.

Other — Other focal neurologic deficits have been described in patients with CMV, including brachial plexus neuropathy, diffuse axonal peripheral neuropathy, transverse myelitis, Horner's syndrome, and cranial nerve palsies

vitamin B12 deficiency

Vitamin B12 (cobalamin) and folate deficiency - Nutritional megaloblastic anemias
The term identifies patients with anemia and macroovalocytic red cells (mean corpuscular volume greater than 100 IL). The bone marrow shows intense erythroid hyperplasia with an abnormal morphology. The megaloblast, the morphologic hallmark of the syndrome, is a product of impaired DNA formation which in turn is due to deficiencies of vitamin B12 (cobalamin, Cbl) or folic acid (FA) . Other causes of impaired DNA or RNA formation, such as antimetabolite drugs and myelodysplastic syndrome, can also lead to megaloblastic anemia.

The neurologic problems, when present, consist of the classic picture of subacute combined degeneration of the dorsal (posterior) and lateral spinal columns. This lesion, specific for Cbl deficiency, is due to a defect in myelin formation of unknown mechanism. The neuropathy is symmetrical and affects the legs more than the arms. It begins with paresthesias and ataxia associated with loss of vibration and position sense, and can progress to severe weakness, spasticity, clonus, paraplegia, and even fecal and urinary incontinence.

Other neurologic abnormalities that can be seen include axonal degeneration of peripheral nerves and central nervous system symptoms including memory loss, irritability, and dementia. Patients may present with Lhermitte's syndrome, a shock-like sensation that radiates to the feet during neck flexion.
Of great clinical importance, not all patients with neurologic abnormalities secondary to Cbl deficiency are either anemic or have macrocytic red cell indices.

A similar neurologic syndrome can be seen in patients with copper deficiency, and the two conditions may coexist. Thus, continued neurologic deterioration in a patient with a history of Cbl deficiency-related myelopathy and normal Cbl levels while receiving Cbl replacement therapy should be evaluated for copper deficiency.

So the question

Clinical features:
- Timing 2/12
- Sensation: loss light touch, reduced vibration bilateral
- Reflexes absent at ankle
- CD4 count 250
- Viral load 5000
- Meds stavudine, lamivudine, nevirapine

A. Guillain-Barré syndrome
Time frame 2/52 – 4/52, weakness major feature

B. HIV-induced neuropathy
Could be but mechanism?

C. cytoegalovirus (CMV) neuropathy
Often GBS

D. ARV-induced neuropathy
Appropriate time frame and clinical picture
Commonly implicated agents include stavudine (d4T) and to a lesser extent didanosine (ddI). The greatest risk was seen with the use of zalcitabine (ddC), which is rarely used by clinicians today

E. vitamin B12 deficiency
Not the most likely from the clinical picture

Answer D