



GUIDE NO. 4

Evaluation of Subacute Headache in Persons with HIV

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ABOUT THIS HIV SYMPTOM EVALUATION GUIDE

The *HIV Symptom Evaluation Guide* addresses the initial diagnostic evaluation of common problems that occur in persons with HIV. The goal of this decision guide is to provide a practical approach to the initial evaluation and diagnosis of subacute headache in persons with HIV.

Clinical judgment should be used to determine whether hospitalization is required. If needed, clinicians should seek expert consultation for assistance with the diagnostic evaluation or management.

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DEFINITION OF SUBACUTE VERSUS PRIMARY HEADACHE

A subacute headache is typically defined as one that has been present intermittently or continuously, for days or several weeks. Although primary headaches (tension, migraine, or cluster) frequently occur in persons with HIV, this guide will focus on secondary causes of headache—those caused by underlying organic abnormality, infection, or medication.

KEY CLINICAL QUESTIONS

Does the individual have meningitis, encephalitis, or focal neurologic deficits?

Symptoms or signs of meningitis or encephalitis, such as fever, nuchal rigidity, altered mental status, blurry vision, and vomiting, should prompt urgent brain imaging and lumbar puncture, regardless of CD4 cell count. New seizure or focal neurologic deficit should also trigger urgent evaluation. Likelihood of specific causes depends on CD4 count.

What is the person's most recent CD4 count?

Current or recent CD4 cell count less than 100 cells/mm³ raises the likelihood of central nervous system (CNS) opportunistic infections (OIs), including cryptococcal meningitis, *Toxoplasma* encephalitis, primary CNS lymphoma, and others. If the CD4 count is less than 100 cells/mm³, it is important to know the *Toxoplasma* IgG status and results of serum cryptococcal antigen testing. Tuberculous CNS disease is more likely at low CD4 cell count. Bacterial (e.g., pneumococcal) and viral infections can occur at any CD4 cell count.

Has syphilis testing been performed recently?

It is important to obtain a sexual history to evaluate risk for syphilis and to review recent syphilis testing results. Neurosyphilis occurs with increased frequency in persons with HIV at any CD4 cell count. Headache from neurosyphilis may occur in conjunction with new visual, hearing, vestibular, or other symptoms and requires urgent evaluation. If serum syphilis testing is positive and any of these symptoms present, lumbar puncture with cerebrospinal fluid (CSF) analysis is indicated.

Are there any skin findings on physical examination?

Secondary syphilis may be complicated by neurosyphilis. Vesicular skin lesions suggest disseminated varicella-zoster virus infection. Disseminated cryptococcal infection can cause diffuse small umbilicated papules resembling molluscum contagiosum or plaque lesions.

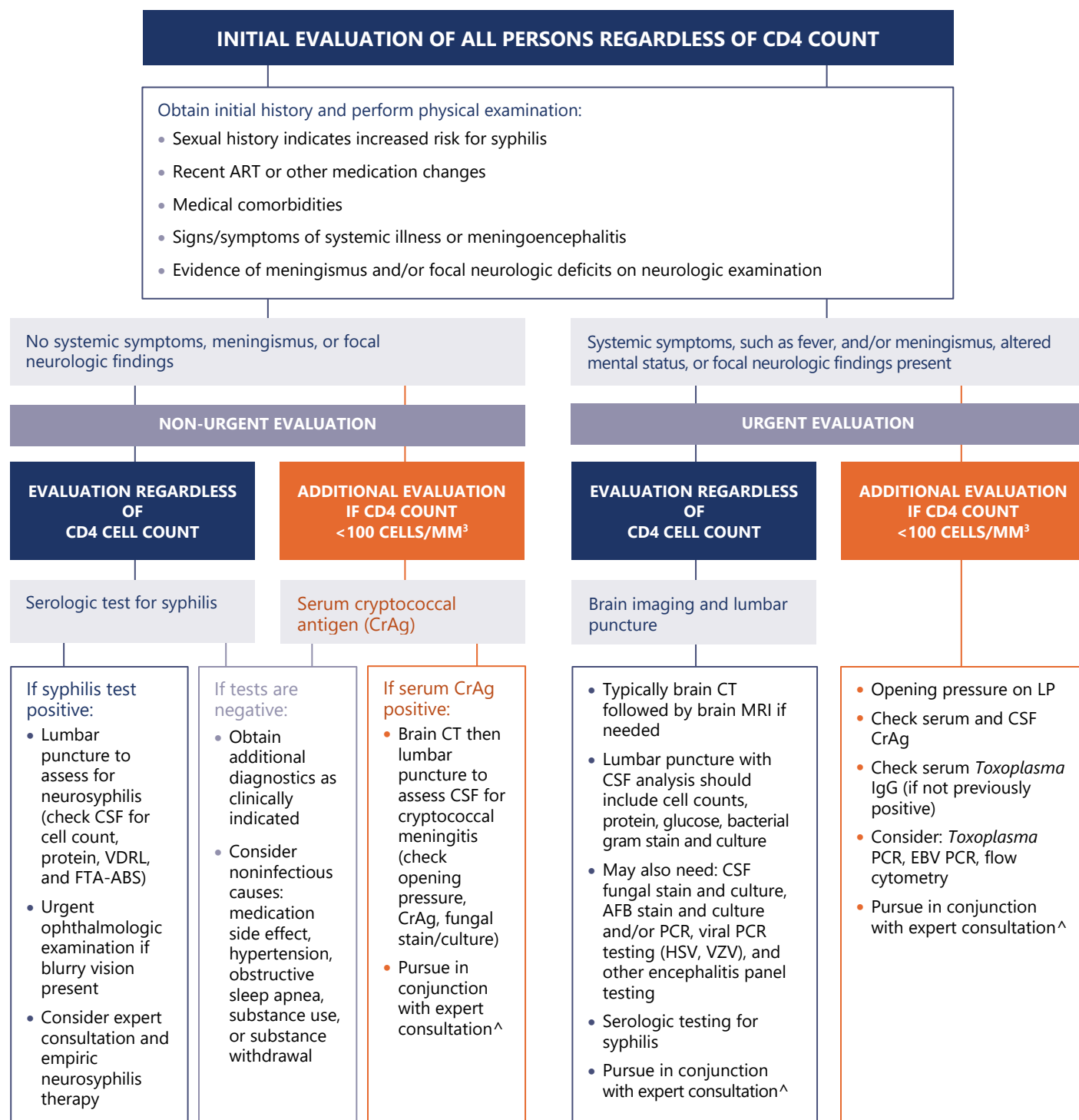
Does the individual have any underlying comorbidities or chronic medical conditions?

At any CD4 count, conditions such as uncontrolled hypertension, obstructive sleep apnea, sinusitis, substance use, or substance withdrawal can lead to headache. Similarly, recent head trauma, especially in persons taking anticoagulant or antiplatelet therapy, raise concern for subdural hematoma.

Were there any recent medication changes?

Certain medications, including the antiretroviral (ART) agents dolutegravir or zidovudine, can cause headache as a side effect, regardless of the CD4 cell count. Non-ART medications, such as oral contraceptives, overuse of pain medications, and others, may cause headache.

DIAGNOSTIC APPROACH TO SUBACUTE HEADACHE IN PERSONS WITH HIV



[^] If local expert consultation is not available, consultation can be obtained through the National Clinician Consultation Center (<http://nccc.ucsf.edu/> or 800-933-3413).

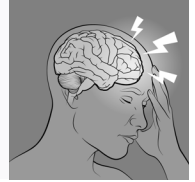
ABBREVIATIONS: AFB = acid fast bacilli; CSF = cerebrospinal fluid; CrAg = cryptococcal antigen; CSF = cerebrospinal fluid; CT = computed tomography; EBV = Epstein-Barr virus; FTA-ABS = fluorescent treponemal antibody absorbed; HSV = herpes simplex virus; LP = lumbar puncture; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; VDRL = venereal disease research laboratory; VZV = varicella zoster virus

COMMON CAUSES AND INITIAL DIAGNOSTIC EVALUATION FOR SUBACUTE HEADACHE IN PERSONS WITH HIV

CAUSE (in alphabetical order)	RISK FACTORS AND CHARACTERISTICS	TYPICAL CD4 CELL COUNT	INITIAL DIAGNOSTIC EVALUATION
Cryptococcal meningitis	Blurry vision, papilledema, nausea, vomiting (signs of elevated ICP), cranial nerve abnormalities Altered mental status; fever Umbilicated papular rash if infection disseminated Can occur with low CSF WBC count	<100 cells/mm ³	Serum CrAg Brain CT then LP for opening pressure, cell counts, CrAg, fungal stain/culture, India Ink or Mucicarmine stain (if available)
Medication side effect	Dolutegravir or zidovudine use Medication overuse (e.g., opiates or caffeine) or withdrawal Aseptic meningitis from NSAIDs or trimethoprim-sulfamethoxazole	Any	None if suspected medication side effect; consider switching ART regimen or discontinuing offending medication If aseptic meningitis suspected, consider LP to rule out other causes
Neurosyphilis	Sexual exposure/condomless sex Blurry vision, hearing changes, tinnitus, balance abnormalities	Any	Serological syphilis testing based on local laboratory algorithm CSF VDRL and/or FTA-ABS with protein, cell count, differential CTA or MRA brain (if stroke-like symptoms or possible CNS vasculitis)
Other infectious meningoencephalitis	Based on clinical history and exam, consider etiologies such as tuberculosis, herpes viruses (HSV, VZV, CMV), arboviruses	Any CD4	Typically brain imaging followed by lumbar puncture Pursue evaluation in conjunction with expert consultation
Other noninfectious etiologies	Consider hypertension, obstructive sleep apnea, substance use, primary brain tumor, subdural hematoma	Any CD4	As indicated by history and exam
Progressive multifocal leukoencephalopathy (PML)	Typically accompanied by other neurologic findings or deficits	<50 cells/mm ³	MRI brain CSF JC virus PCR
Primary CNS lymphoma	Advanced HIV Altered mental status, seizures and/or focal deficits	<100 cells/mm ³	MRI brain CSF EBV PCR CSF cytology and flow cytometry Brain biopsy, if indicated
<i>Toxoplasma</i> encephalitis	Positive serum <i>Toxoplasma</i> IgG Seizures, altered mental status, focal deficits and/or fever	<100 cells/mm ³	MRI brain Serum <i>Toxoplasma</i> IgG CSF <i>Toxoplasma</i> PCR Brain biopsy (typically after trial of empiric therapy)

ABBREVIATIONS: ART = antiretroviral therapy; CrAg = cryptococcal antigen; CMV = cytomegalovirus; CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; CTA = computed tomography angiography; EBV = Epstein-Barr Virus; FTA-ABS = fluorescent treponemal absorption antibody test; HSV = herpes simplex virus; ICP = intracranial pressure; LP = lumbar puncture; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; NSAIDs = non-steroidal anti-inflammatory medications; PCR = polymerase chain reaction; VDRL = venereal disease research laboratory test; VZV = varicella zoster virus

KEY SUMMARY POINTS



- The first step in the evaluation of a subacute secondary headache is to assess whether there are associated signs or symptoms of meningoencephalitis, focal neurologic deficits, or new seizure activity; if any are present, urgent evaluation is needed, typically with brain imaging with contrast followed by lumbar puncture and CSF analysis. Always consider causes that can occur at any CD4 cell count, including bacterial meningitis, viral encephalitis, or brain malignancy.
- It is essential to ascertain the current or most recent CD4 count. A CD4 count less than 100 cells/mm³ indicates risk for serious CNS opportunistic infections, including cryptococcal meningitis, toxoplasma encephalitis, and CNS lymphoma. Cryptococcal meningitis most often occurs at CD4 count below 100 cells/mm³, but occasionally at higher levels.
- Cryptococcal meningitis may not cause classic signs of meningismus, such as neck stiffness, and may manifest simply as subacute headache and fever. The evaluation for cryptococcal meningitis should consist of brain CT followed by lumbar puncture (with opening pressure measurement). A low CSF neutrophil count does not rule out cryptococcal meningitis. Confirming the diagnosis may require serum and CSF cryptococcal antigen, plus CSF fungal culture or India ink or Mucicarmine stain (if available). If there is high suspicion for cryptococcal meningitis and the cryptococcal antigen test is negative, the specimen may need to be diluted and retested.
- *Toxoplasma* encephalitis is a reactivation disease that occurs in persons who have advanced HIV and positive serum *Toxoplasma* antibody. The diagnosis is suggested by ring-enhancing lesions on brain CT or MRI (usually multiple, but a solitary lesion may occur). *Toxoplasma* PCR testing of CSF has limited value due to low sensitivity. With suspected *Toxoplasma* encephalitis, brain biopsy is usually limited to persons who fail empiric therapy.
- Individuals with a CD4 count less than 100 cells/mm³ and ring-enhancing lesions on brain imaging may have primary CNS lymphoma (usually a solitary lesion but multiple lesions does not rule out the diagnosis). Diagnostic modalities include MRI with gadolinium, positron emission tomography (PET) or single-photon emission computerized tomography (SPECT) scan, CSF analysis (EBV PCR, cytology, and flow cytometry), and brain biopsy. This diagnosis should be considered in a person for whom CNS toxoplasmosis is suspected but has not had a clinical or radiologic response to toxoplasmosis treatment. In addition, a solitary brain lesion confirmed by MRI significantly increases the likelihood of primary CNS lymphoma and should prompt consideration of an early biopsy instead of waiting for response to treatment for toxoplasmosis. Brain biopsy is usually necessary to confirm the diagnosis of CNS lymphoma before initiating lymphoma therapy.
- Neurosyphilis can cause headache and can occur at any stage of syphilis and at any CD4 cell count. All persons with HIV should be screened for syphilis. Individuals with evidence of new or recurrent syphilis should be asked about neurologic symptoms, including headache, and considered for lumbar puncture if present. Accompanying ocular symptoms should trigger urgent ophthalmologic evaluation.
- At any CD4 cell count, a person with HIV may develop subacute headache of a noninfectious cause. Common culprits include medication overuse or medication side effect; of the antiretroviral medications, dolutegravir or zidovudine are the most likely to cause headache. Other common etiologies include uncontrolled hypertension, obstructive sleep apnea, substance use or substance withdrawal, head trauma, brain tumor, and others.

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