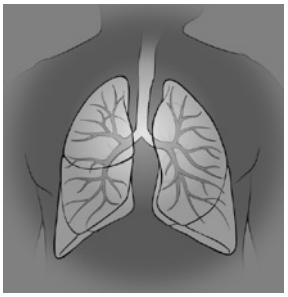

GUIDE NO. 1

Evaluation of Cough and Dyspnea in Persons with HIV

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Gretchen Snoeyenbos Newman, MD[3] / Ronald D. Wilcox, MD[4] / David H. Spach, MD[1]

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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 acute or subacute cough and dyspnea 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.

PERMISSIONS

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September 15, 2022

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THIS PROJECT WAS FUNDED BY THE HEALTH RESOURCES AND SERVICES ADMINISTRATION.

DEFINITIONS OF ACUTE VERSUS CHRONIC SYMPTOMS

Cough is generally considered acute if it develops over a time period shorter than 3 weeks and subacute if over a duration of 3 to 8 weeks. Dyspnea is typically considered acute if it develops over a period of hours to days and subacute if over a period of 4 to 8 weeks. This symptom guide topic will not address chronic cough or chronic dyspnea.

KEY CLINICAL HISTORY

What is the current local Covid-19, influenza, and other respiratory viral activity?

Knowledge of local and regional viral respiratory illness epidemiology, most notably Covid-19 and influenza, should inform the initial evaluation and diagnostic testing. It is important to assess the person's likelihood of exposure and inquire about recent contacts with sick persons. Rhinorrhea, sore throat, and muscle aches make viral respiratory infection more likely. A history of recent viral pneumonia may suggest secondary bacterial infection with *Streptococcus pneumoniae* or *Staphylococcus aureus*.

What is the person's most recent CD4 cell count?

Knowledge of the individual's CD4 cell count is a critical factor in whether to consider HIV-related causes. Persons with HIV have an increased risk of pneumococcal pneumonia and tuberculosis at any CD4 count, and these risks increase with CD4 counts less than 500 cells/mm^3. A current or recent CD4 count less than 200 cells/mm^3 raises the likelihood of Pneumocystis pneumonia (PCP), caused by *Pneumocystis jirovecii*, especially if the individual is not taking PCP prophylaxis and has a detectable HIV RNA level. With a CD4 count less than 100 cells/mm^3, certain opportunistic infections and malignancies are more likely, such as opportunistic endemic fungal infections and pulmonary Kaposi sarcoma.

If the CD4 count is less than 200 cells/mm^3, is the individual taking PCP prophylaxis?

Adherence to PCP prophylaxis, such as trimethoprim-sulfamethoxazole, markedly reduces the likelihood of PCP. If the person is taking dapsone for prophylaxis, methemoglobinemia and hemolytic anemia should be considered as possible causes of dyspnea.

Are there associated systemic symptoms or mucocutaneous manifestations?

Associated generalized symptoms, such as weight loss and night sweats, raise suspicion for tuberculosis, disseminated fungal infection, or malignancy. Associated skin or mucosal lesions may suggest disseminated fungal infection or Kaposi sarcoma.

Has the individual received routine vaccinations?

Vaccination to prevent *Streptococcus pneumoniae*, Covid-19, or influenza makes these infections less likely, but prior vaccination does not rule out infection. It is important to note that persons with HIV may have diminished vaccine responses, especially those who have a CD4 count less than 200 cells/mm^3.

Does the person have a history of smoking or non-infectious lung conditions?

COPD and lung cancer are more common in persons with HIV, as are other non-infectious cardiac and pulmonary conditions. Flares of asthma, congestive heart failure (CHF), or pulmonary hypertension (HTN) should be considered with compatible clinical history and exam. Other non-infectious etiologies, including gastroesophageal reflux disease (GERD), post-nasal drip, angiotensin-converting enzyme (ACE) inhibitors, and bronchiectasis, may trigger a subacute cough.

DIAGNOSTIC APPROACH TO ACUTE OR SUBACUTE COUGH OR DYSPNEA IN PERSONS WITH HIV

INITIAL EVALUATION OF ALL PERSONS REGARDLESS OF CD4 COUNT

Obtain history and evaluate symptoms:

Local Covid-19 and influenza activity; sick contacts; travel; time spent in areas with specific endemic fungi; TB exposure or risk factors; medications; smoking history; associated symptoms

Exposure risk and symptoms compatible with respiratory viral infection

- Nasopharyngeal PCR for Covid-19, influenza/RSV (full PCR panel for other respiratory viruses rarely indicated)
- If negative and high suspicion, CXR, chest CT, and/or bronchoscopy with BAL for PCR may be indicated

Symptoms and history compatible with bacterial pneumonia

- CBC/differential, CXR
- If hospitalized: blood and sputum culture; urine *S. pneumoniae* antigen; and consider Legionella urine antigen
- If above negative, with compatible clinical syndrome, consider chest CT, bronchoscopy/BAL

Systemic symptoms with history of possible TB exposure

- Sputum AFB cultures and PCR (per local protocol); obtain induced sputum if unable to generate expectorated samples
- Pleural fluid culture and/or PCR if pleural effusion and sputum tests negative
- Bronchoscopy with BAL if above evaluation negative; biopsy of other tissue (e.g., lymph node if lymphadenopathy present)

REVIEW RESULTS AND REEVALUATE

If evaluation negative, consider other less common causes and/or noninfectious causes (see table)

Obtain expert consultation^ if symptoms persist and diagnosis remains uncertain

ADDITIONAL EVALUATION IF CD4 COUNT <200 CELLS/MM^3

For *Pneumocystis* pneumonia:

- CXR
- Consider chest CT
- Ambulatory SaO2 and arterial blood gas (ABG)
- Induced sputum for *Pneumocystis* stain/DFA
- Blood beta-D-glucan if available
- If induced sputum is negative: bronchoscopy with BAL for *Pneumocystis* stain/DFA

If taking dapsone and clinical syndrome compatible with methemoglobinemia:

- ABG with methemoglobin level; blood co-oximetry

REVIEW RESULTS AND REEVALUATE

If evaluation negative:

- Consider other less common infectious causes and/or noninfectious causes
- Obtain expert consultation^ if symptoms persist and diagnosis remains uncertain

^ 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; ABG = arterial blood gas; BAL = bronchoalveolar lavage; CBC = complete blood counts; CT = computed tomography; CXR = chest x-ray; DFA = direct fluorescent antibody; PCR = polymerase chain reaction; RSV = respiratory syncytial virus; TB = tuberculosis

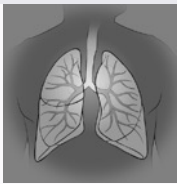
COMMON CAUSES AND INITIAL DIAGNOSTIC EVALUATION FOR ACUTE OR SUBACUTE COUGH AND/OR DYSPNEA IN PERSONS WITH HIV

CAUSE (in alphabetical order)	RISK FACTORS AND CHARACTERISTICS	TYPICAL CD4 CELL COUNT	INITIAL DIAGNOSTIC EVALUATION (in addition to CBC with differential and CXR)*
Bacterial pneumonia: Typical (*S. pneumoniae*, *Haemophilus*, *Moraxella*), or atypical (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella*) and *Bordetella pertussis*. Also increased in HIV: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Rhodococcus equi*.	Similar to individuals without HIV (lobar infiltrate more likely with typical pathogen, reticulonodular or patchy infiltrates more likely with atypical) *Legionella*: hyponatremia, transaminitis, high LDH, and GI symptoms	Any	Sputum and blood cultures (if hospitalized) *S. pneumoniae* urine antigen Consider *Legionella* urine antigen Consider *Bordetella pertussis* PCR
Fungal pneumonia: *Pneumocystis* pneumonia (PCP), endemic fungal infection (*Histoplasma, Coccidioides, Blastomyces,* etc.)	PCP: low CD4 and not receiving prophylaxis *Histoplasma, Coccidioides, Blastomyces*: time spent in endemic area; peripheral eosinophilia (especially with *Coccidioides*); skin or mucosal lesions	PCP: <200 cells/mm^3 Other: any	PCP: ambulatory Sa02, ABG, induced sputum stain, beta-D-glucan (if available); bronchoscopy with BAL for staining, DFA, or PCR^ Other endemic fungi: urine *Histoplasma Ag*, serum *Coccidioides* antibody
Herpes viruses: Kaposi sarcoma (KS) caused by HHV-8 virus; rarely other herpes viruses (e.g., CMV, HSV, VZV)	Pulmonary KS: often with compatible skin or mucosal lesions; nodular disease on CXR or CT Interstitial pneumonia from other herpes viruses: rare and often associated with systemic or cutaneous symptoms	KS: any (though more likely if <50–100 cells/mm^3) CMV: <50 cells/mm^3	KS: Bronchoscopy (to visualize lesions); biopsy skin lesion. Do NOT biopsy pulmonary KS lesions. CMV: Bronchoscopy with lung biopsy (diagnosis requires compatible pathology)
Medication-related: Methemoglobinemia secondary to dapsone (used for PCP prophylaxis)	Cyanosis but PaO2 may be normal Blood has chocolate-like appearance	Typically <200 cells/mm^3	Dyspnea may be acute or subacute Blood co-oximetry panel for methemoglobin levels
Mycobacterial pneumonia: *M. tuberculosis*; less often other species (e.g., MAC or *M. kansasii*)	Exposure risk; prior positive TST or IGRA Not ruled out if negative TST or IGRA (especially if low CD4)	Any: atypical and disseminated disease most likely if <200 cells/mm^3	Sputum AFB stain and cultures, sputum PCR (or nucleic acid amplification test) Blood AFB culture if systemic symptoms
Noninfectious: COPD or CHF exacerbation, lung cancer, etc.	Similar to persons without HIV	Any	Same evaluations as persons without HIV
Respiratory Viruses: Covid-19, influenza, RSV, others	Similar to persons without HIV	Any; severity may be worse if <200 cells/mm^3	Nasopharyngeal PCR

* The common initial evaluation is listed here. If high clinical suspicion exists yet evaluation is negative, expert consultation is recommended.
^ PCR is highly sensitive but may not accurately distinguish colonization from active disease.

ABBREVIATIONS: ABG = arterial blood gas; AFB = acid-fast bacilli; Ag = antigen; CMV = cytomegalovirus; COPD = chronic obstructive pulmonary disease; CXR = chest X-ray; HHV-8 = human herpesvirus-8; HSV = herpes simplex virus; IGRA = interferon-gamma release assay; MAC = *Mycobacterium avium* complex; PCR = polymerase chain reaction; RSV = respiratory syncytial virus; TST = tuberculin skin test; VZV = varicella-zoster virus

KEY SUMMARY POINTS



- There are four main considerations when conducting an initial evaluation of acute or subacute cough and/or dyspnea in a person with HIV, we consider four main types of causes: (1) viral respiratory pathogens, such as Covid-19 and influenza, (2) community-acquired bacterial pneumonia, (3) HIV-related opportunistic infections, particularly Pneumocystis pneumonia (PCP) for those with advanced immunosuppression, and (4) non-infectious causes.
- A thorough clinical history should always be obtained that includes a review of associated symptoms, the most recent CD4 cell count, recent close contact with a sick individual, and medications. Knowledge of local and regional viral respiratory illness epidemiology may impact the diagnostic evaluation.
- The diagnostic evaluation depends on the CD4 cell count and pre-test probability of certain infections, with a typical initial evaluation including a CBC with differential and a chest X-ray. Further evaluation may be required, including obtain sputum for cultures and/or PCR testing, chest CT, bronchoscopy, and rarely, lung biopsy. Tests for specific etiologies may be indicated based on exposures.
- Infection with common respiratory bacterial or viral pathogens can occur at any CD4 cell count. Some bacterial pneumonia pathogens, such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, occur more frequently in persons with HIV, especially those with low CD4 cell counts.
- Individuals with a CD4 count less than 200 cells/mm^3 are at risk for opportunistic pulmonary infections, most commonly *Pneumocystis* pneumonia (PCP), which is also referred to as *Pneumocystis jirovecii* pneumonia (PJP). Less frequent HIV-related causes of respiratory illness include endemic fungal infections (e.g., *Coccidioides*, *Histoplasma*, and *Blastomyces*) and pulmonary Kaposi sarcoma.
- Symptoms and signs in persons with PCP usually develop over several weeks and commonly include fever, dry cough, dyspnea, and hypoxia that worsens with exertion. Chest X-ray typically shows diffuse interstitial infiltrates, but a normal chest x-ray does not rule out PCP. An arterial blood gas helps determine optimal treatment, including whether concomitant corticosteroid therapy should be administered. Diagnosis generally relies on staining or PCR of respiratory samples. Sputum should be induced to obtain a sample for testing; expectorated sputum has very low sensitivity. If an induced sputum is negative, bronchoalveolar lavage should be performed.
- *Mycobacterium tuberculosis* pulmonary infection occurs with increased frequency in persons with HIV at any CD4 cell count, but the risk is highest with a low CD4 cell count. With a CD4 count less than 200 cells/mm^3, chest imaging may be atypical, without upper lobe involvement or cavitations. Tuberculin skin test or interferon-gamma release assay are not appropriate for the evaluation of active pulmonary tuberculosis. The diagnosis is made presumptively with a positive sputum AFB smear and definitively with molecular tests and culture of sputum.
- *Mycobacterium avium complex* (MAC) may cause pulmonary infection in persons with HIV; most often, identification of MAC in respiratory secretions signifies lung colonization, but in persons with a CD4 count less than 50 cells/mm^3, MAC can rarely cause pulmonary disease.
- Noninfectious causes of cough and dyspnea should be considered based on medical history such as cardiac causes, COPD, CHF, pulmonary HTN, pulmonary embolus, and others.

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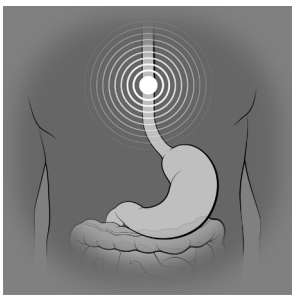

GUIDE NO. 2

Evaluation of Odynophagia in Persons with HIV

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Gretchen Snoeyenbos Newman, MD[3] / Ronald D. Wilcox, MD[4] / David H. Spach, MD[1]

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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 odynophagia 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.

PERMISSIONS

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September 15, 2022

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DEFINITION OF ACUTE ODYNOPHAGIA

Odynophagia is typically defined as retrosternal chest pain felt with or just after swallowing; acute odynophagia is defined as symptoms present for less than 14 days.

KEY CLINICAL QUESTIONS

Does the individual have odynophagia or pharyngitis?

It is important to first clarify if the person's symptoms originate from the esophagus, the pharynx, or both. Individuals with an esophageal disorder typically present with odynophagia (retrosternal chest pain felt with or just after swallowing) and/or dysphagia (difficulty swallowing, with a sensation of food sticking in the throat or chest). In contrast, discomfort originating from the pharynx will usually be described as discomfort in the throat region.

What is the person's most recent CD4 cell count?

Current or recent low CD4 cell count raises the likelihood of certain HIV-associated disorders that may cause odynophagia. In persons with a CD4 count less than 100 cells/mm^3, HIV-related causes include esophageal candidiasis, herpes simplex virus (HSV)-related ulcerations, and gastrointestinal Kaposi sarcoma. If the CD4 count is less than 50 cells/mm^3, additional consideration should include cytomegalovirus (CMV)-induced ulcers and aphthous lesions (ulcers). Oral candidiasis, or oral thrush, may occur at CD4 less than 200 cells/mm^3, but esophageal involvement typically occurs only when the CD4 declines to less than 100 cells/mm^3.

Does the individual have a history of gastroesophageal reflux?

Gastroesophageal reflux is a common cause of odynophagia and can occur at any CD4 cell count. It is important to know if the person has classic "heartburn" symptoms or a past diagnosis of reflux disease. A history of worsening symptoms when recumbent and/or a history of response to acid-suppressive therapy supports the diagnosis of reflux disease.

Has the person swallowed any toxic substances?

Although most individuals would provide this history, it is important to rule out intentional (or unintentional) ingestion of substances, such as cleaning products or bleach, that could cause esophagitis.

Has the person recently taken any oral medication known to cause pill esophagitis?

Certain oral medications, such as aspirin, bisphosphonates, doxycycline (and tetracycline), iron, nonsteroidal anti-inflammatory drugs (NSAIDs), or potassium chloride, can cause pill esophagitis and odynophagia.

Are there any abnormalities on oral examination?

Esophageal candidiasis is by far the most common cause of odynophagia in persons living with HIV who have a CD4 count less than 100 cells/mm^3, and the presence of oral candidiasis is a good predictor of esophageal candidiasis in persons with odynophagia but is not diagnostic of esophageal involvement. Similarly, the presence of oral HSV lesions makes the presence of this disorder in the esophagus more likely, but diagnosis is usually through endoscopy.

DIAGNOSTIC APPROACH TO ODYNOPHAGIA IN PERSONS WITH HIV

INITIAL EVALUATION OF ALL PERSONS REGARDLESS OF CD4 COUNT

Obtain initial history and perform physical examination:

- History of toxic ingestion
- Symptoms or history of reflux
- Taking medication known to cause pill esophagitis
- Abnormalities on oropharyngeal examination

Toxic ingestion

Immediate referral to specialist and request for endoscopy

Symptoms compatible with reflux

Empiric trial with acid-suppressing therapy; always assess for drug interactions with antiretrovirals

Suspected pill esophagitis

Severe symptoms:

Refer for endoscopy

Mild symptoms:

Discontinue offending medication if possible

ADDITIONAL STEPS IF CD4 COUNT <100 CELLS/MM^3

If no cause already identified:

- Initiate empiric treatment for esophageal candidiasis with oral fluconazole (if not pregnant)*

REVIEW RESULTS AND REEVALUATE IN 3–7 DAYS

If symptoms improved:

Complete 14- to 21-day course of oral fluconazole or other systemic antifungal

If symptoms not improved:^

Prompt referral to GI specialist for EGD. Testing via EGD should include:

- Fungal stain and culture of any superficial white lesions
- Biopsy of any ulcerative lesions to evaluate tissue pathology for CMV and to perform HSV PCR test

* Treating esophageal candidiasis during pregnancy should be done in consultation with an expert due to potential teratogenicity from fluconazole and other systemic antifungal drugs.

^ 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).

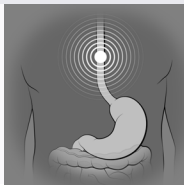
ABBREVIATIONS: CMV = cytomegalovirus; EGD = esophagogastroduodenoscopy; GI = gastrointestinal; HSV = herpes simplex virus; PCR = polymerase chain reaction

COMMON CAUSES AND INITIAL DIAGNOSTIC EVALUATION FOR ODYNOPHAGIA IN PERSONS WITH HIV

CAUSE (in alphabetical order)	RISK FACTORS AND CHARACTERISTICS	TYPICAL CD4 CELL COUNT	INITIAL DIAGNOSTIC EVALUATION
Acid reflux	Heartburn symptoms History of reflux Worse when recumbent and after eating certain foods	Any	Response to empiric treatment, dietary modifications, and/or lifestyle changes Characteristic findings on endoscopy
Aphthous lesion(s)	Cause/trigger unknown Typically, 1–2 large esophageal ulcers	<50 cells/mm^3	Visible ulcer(s) on endoscopy without identifiable cause Biopsy shows inflammatory cells Diagnosis of exclusion
Candida esophagitis	Multiple yellow-white esophageal patches and plaques Oral candidiasis usually present (but not always)	<100 cells/mm^3	Response to empiric treatment Visual appearance on endoscopy +/- confirmation with culture
Cytomegalovirus (CMV)	Typically, 1–2 large esophageal ulcers CMV retinitis often present	<50 cells/mm^3	Endoscopy with biopsy: Diagnosis confirmed by tissue sample showing inclusion bodies Diagnosis should not be made based on culture or PCR alone
Herpes simplex virus (HSV)	Multiple small, shallow esophageal ulcers or vesicles May have concurrent orolabial ulcers	<100 cells/mm^3	Endoscopy with biopsy: Sample should include HSV PCR and culture
Pill esophagitis	Recent ingestion of medication known to cause esophagitis Improvement with ingesting pill with a large glass of water or after discontinuing medication	Any	Endoscopy with one or more findings: Solitary ulcer or kissing ulcers Mucosal erythema and erosion Bleeding ulcer Ulcer with visible medication coating
Toxic ingestion	Severe acute pain following ingestion	Any	Immediate evaluation and expert referral if toxic ingestion suspected Prompt endoscopy to evaluate severity of esophageal damage

ABBREVIATIONS: PCR = polymerase chain reaction

KEY SUMMARY POINTS



- It is important to distinguish odynophagia—typically described as retrosternal pain felt after swallowing—from other similar symptoms, including dysphagia (difficulty swallowing), pharyngeal disorders (e.g., pharyngitis, tonsillitis, retropharyngeal abscess), and chest pain, including from cardiac origin. The causes of odynophagia and dysphagia overlap, and a person may experience both concurrently.
- Persons living with HIV most often develop odynophagia from causes not related to HIV, such as gastroesophageal reflux and pill esophagitis.
- The most common HIV-related causes of odynophagia are esophageal candidiasis and HSV-associated esophageal ulcers; these typically occur only in persons with a CD4 count less than 100 cells/mm^3. In addition, persons with a CD4 count less than 50 cells/mm^3 may develop CMV-induced ulcers or aphthous lesions. The most common etiology when the CD4 cell count is low is esophageal candidiasis.
- Unless the history indicates a clear alternate cause of the odynophagia, the initial recommended approach in a person with HIV and a CD4 count less than 100 cells/mm^3 is to empirically treat for esophageal candidiasis with systemic antifungal therapy (such as fluconazole, assuming the individual is not pregnant). This approach has both diagnostic and treatment utility.
- Persons with a CD4 count less than 100 cells/mm^3 who do not respond to antifungal therapy within 3 to 7 days should be promptly referred for gastroesophageal endoscopy. The endoscopic procedure should include a biopsy of any visible ulcers. Ulcers caused by CMV and aphthous lesions are typically large and few in number, whereas HSV-related ulcers typically are generally small and numerous.
- For persons who have dysphagia (difficulty swallowing food and/or the sensation of food stuck in the chest), the most common causes (at any CD4 cell count) include esophageal stricture, esophageal cancer, or eosinophilic esophagitis. Gastrointestinal Kaposi sarcoma, which is caused by the human herpesvirus-8, can cause esophageal lesions and gastrointestinal bleeding but typically only occurs in persons with a CD4 count less than 100 cells/mm^3. Diagnosis of all of these causes requires endoscopy.

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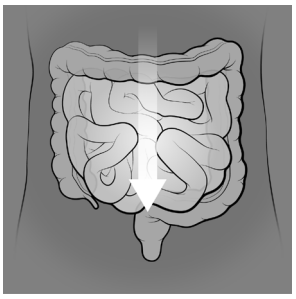

GUIDE NO. 3

Evaluation of Acute Diarrhea in Persons with HIV

Gretchen Snoeyenbos Newman, MD[1] / Brian R. Wood, MD[2] / Jehan Z. Budak, MD[2] / Aley G. Kalapila, MD[3] / Ronald D. Wilcox, MD[4] / David H. Spach, MD[2]

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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 acute or subacute cough and dyspnea 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.

PERMISSIONS

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DEFINITIONS OF ACUTE VERSUS CHRONIC DIARRHEA

Diarrhea is defined as loose or watery bowel movements that occur 3 or more times per day or passage of a greater number of stools of decreased form compared to normal. Acute diarrhea, by definition, has been present for 14 days or less. Diarrhea present for 15 to 30 days is referred to as persistent and greater than 30 days as chronic. This guide will focus on causes of acute diarrhea; occasionally, etiologies described here may cause symptoms that last greater than 14 days (symptoms may be prolonged in the setting of a CD4 count below 200 cells/mm^3).

KEY CLINICAL HISTORY

What is the person's most recent CD4 cell count?

Current or recent low CD4 cell count indicates risk for certain opportunistic infections (OIs), such as cryptosporidiosis (CD4 count less than 200 cells/mm^3), cytomegalovirus (CMV) colitis (CD4 count less than 50 cells/mm^3), or disseminated *Mycobacterium avium* complex (MAC) infection (CD4 count less than 50 cells/mm^3).

Does the individual have bloody diarrhea, fever, or other associated symptoms?

Bloody diarrhea, especially associated with fever, suggests a potentially serious infection with a bacterial enteric pathogen or CMV colitis if the CD4 count is less than 50 cells/mm^3. Fever, in conjunction with systemic symptoms and weight loss, especially in the setting of a recent CD4 count less than 50 cells/mm^3, raises the likelihood of disseminated MAC infection. Fever or respiratory symptoms along with diarrhea may suggest COVID-19 illness at any CD4 cell count.

Have any recent sexual exposures occurred?

It is important to obtain recent sexual history since bacterial enteric infections can be transmitted among persons who have condomless anal sex or oral-anal contact. Rectal sex raises the risk of enteric bacterial infections (e.g., *Campylobacter sp.* and *Shigella sp.*), *Giardia* infection, and chlamydia proctitis (lymphogranuloma venereum [LGV] serovars).

Recently, has there been any of the following: close contact with a person who was sick, ingestion of contaminated food, travel outside the United States, or antibiotic use?

Viral gastroenteritis is commonly transmitted among close contacts. Exposure to contaminated foods may lead to the transmission of diarrheal pathogens. Recent antibiotic use or hospitalization are risk factors for *Clostridioides difficile*-associated diarrhea.

Were there any recent changes in antiretroviral therapy medications?

Certain antiretroviral medications, particularly protease inhibitors and boosting agents (ritonavir and cobicistat), can cause diarrhea and other gastrointestinal symptoms.

Is the person living homeless? If so, do they have documented immunity to hepatitis A?

There have been recent outbreaks of hepatitis A infection, especially in individuals living homeless. Persons who have oral-anal sexual contact also are at increased risk.

DIAGNOSTIC APPROACH TO ACUTE DIARRHEA IN PERSONS WITH HIV

INITIAL EVALUATION OF ALL PERSONS REGARDLESS OF CD4 COUNT

Obtain recent exposure history:

Sick contacts, sexual exposures, antibiotics, hospitalization, dietary, travel, new ARVs/meds

Obtain review of symptoms and perform physical examination:

If respiratory symptoms, consider COVID-19 illness

Multiplex enteric stool PCR panel available:

Test one stool sample with multiplex PCR panel assay:

- Detects most of the common viral, bacterial, and protozoal diarrheal pathogens
- Not used for diagnosis of CMV or MAC

Blood culture:

- Also obtain blood culture if febrile and acutely ill

Multiplex enteric stool PCR panel NOT available:

Test one stool sample for:

- Culture for enteric bacterial pathogens
- *C. difficile* (if recent antibiotics or hospitalization)
- *Giardia* (if supported by symptoms and exposure history)
- Viral PCR (if sick contacts and/or outbreak)

Test three stool samples for:

- Ova and parasite exam (O&P) if history of recent travel

Blood culture:

- Also obtain blood culture if febrile and acutely ill

REVIEW RESULTS AND REEVALUATE

If testing positive:

- Provide targeted therapy as indicated

If testing negative:

- Obtain additional diagnostics as clinically indicated, including abdominal imaging and referral for colonoscopy (if not already done)
- Consider medication as cause
- Obtain expert consultation^ if symptoms persist and diagnosis remains uncertain

ADDITIONAL EVALUATION IF CD4 COUNT <200 CELLS/MM^3

If non-bloody diarrhea:

- Obtain diagnostic tests for cryptosporidium, cyclospora, and cystoisospora with either multiplex enteric PCR or modified AFB stain

If CD4 count <50 cells/mm^3 and bloody stools:

- Refer to GI specialist for colonoscopy with biopsy to test for CMV

If CD4 count <50 cells/mm^3 and systemic symptoms (such as fever and weight loss):

- Obtain AFB blood culture to test for disseminated MAC

REVIEW RESULTS AND REEVALUATE

If evaluation diagnostic positive:

- Provide targeted therapy as indicated

If evaluation diagnostic negative:

- Obtain additional diagnostics as clinically indicated, including abdominal imaging and referral for colonoscopy (if not already done)
- Consider medication as cause
- Obtain expert consultation^ if symptoms persist and diagnosis remains uncertain

^ 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).

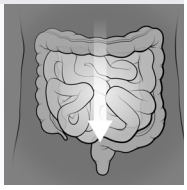
ABBREVIATIONS: AFB = acid-fast bacilli; ARV = antiretroviral; CMV = cytomegalovirus; GI = Gastroenterology; MAC = *Mycobacterium avium* complex; PCR = polymerase chain reaction

COMMON CAUSES AND INITIAL DIAGNOSTIC EVALUATION FOR ACUTE DIARRHEA IN PERSONS WITH HIV

CAUSE (in alphabetical order)	RISK FACTORS AND CHARACTERISTICS	TYPICAL CD4 CELL COUNT	INITIAL DIAGNOSTIC EVALUATION
Clostridioides difficile (*C. diff.*)	Antibiotic or healthcare exposure Typically, watery diarrhea often accompanied by pain	Any	PCR +/- EIA for glutamate dehydrogenase, or toxin A/B; algorithm may vary by institution
Cytomegalovirus (CMV) colitis	Advanced HIV Often bloody diarrhea with abdominal pain and systemic symptoms	<50 cells/mm^3	Colonoscopy *with biopsy* and pathology Diagnosis should not be made based on stool culture or PCR of stool or blood alone
Disseminated *Mycobacterium avium* complex (MAC)	Advanced HIV Associated with systemic symptoms and weight loss	<50 cells/mm^3	Blood AFB culture Diagnosis should not be made based on stool PCR or stool culture (stool culture supportive but not diagnostic)
Enteric bacterial pathogens: *Campylobacter*, *Shigella* species; *Salmonella* species; toxigenic *E. coli* strains	Sexual exposure (primarily rectal sex), food exposure, travel to resource-limited setting Liquid, watery, or bloody diarrhea	Any	Stool enteric multiplex PCR, if available If multiplex PCR NOT available, order stool culture Obtain blood culture if systemically ill
Medication-related	New medication that may cause diarrhea	Any	Other causes ruled out Most common ART: boosting agents (ritonavir and cobicistat) and protease inhibitors
Protozoal infections: *Giardia*, cryptosporidium, cyclospora, cystoisospora, *Entamoeba histolytica*	*Giardia*: travel, sexual exposure Others: travel, local outbreaks Typically, watery diarrhea that may persist for >14 days	Any	Stool enteric multiplex PCR, if available If multiplex PCR NOT available, order all of the following: Cryptosporidium, cyclospora, cystoisospora: stool modified AFB stain (not detected with O&P test); DFA also available in some labs for cryptosporidium *E. histolytica*: antigen or PCR *Giardia*: stool antigen test or PCR
Viral gastroenteritis pathogens: Norovirus (Norwalk virus), rotavirus, enteric adenovirus, SARS CoV-2 (COVID-19)	Group living setting, local outbreaks, food exposure Typically, watery diarrhea Associated respiratory symptoms with COVID-19	Any	Stool enteric multiplex PCR, if available, or Stool viral-specific PCR Respiratory PCR swab if SARS CoV-2 infection suspected

ABBREVIATIONS: AFB = acid-fast bacilli; ART = antiretroviral therapy; EIA = enzyme immunoassay; O&P = ova and parasites; PCR = polymerase chain reaction

KEY SUMMARY POINTS



- For an initial evaluation of acute diarrhea in a person with HIV, consider three main causes: (1) common viral or bacterial infections that are not unique to HIV and may be related to local outbreaks or to sexual transmission, (2) opportunistic gastrointestinal infections that occur in the setting of advanced CD4 T-cell depletion, and (3) noninfectious causes, such as recent ART or other medication or dietary changes.
- At any CD4 count, individuals may contract viral gastroenteritis or may acquire bacterial enteric infections, such as *Campylobacter* or *Shigella*. Bacterial enteric infections may be acquired through sexual contact, particularly anal sex and oral-anal contact.
- The most important causes of diarrhea that occur in persons with HIV and advanced immunosuppression (CD4 less than 50–100 cells/mm^3) are cryptosporidiosis, disseminated MAC, and CMV colitis.
- Most viral, bacterial, and parasitic pathogens that cause diarrhea in persons with HIV can be identified on a single stool specimen using a multiplex enteric PCR panel. This test, if available, is highly sensitive and specific and can provide results within 24 hours. However, the multiplex enteric PCR tests should not be used to diagnose CMV or MAC.
- If a multiplex enteric PCR panel is not available, the diagnostic evaluation should consider specific epidemiologic factors and laboratory tests tailored to detect likely pathogens. For example, a stool ova and parasite (O&P) exam is not sufficient to detect cryptosporidium or similar pathogens, so a separate examination of the stool must be requested.
- The diagnosis of CMV colitis requires a compatible clinical syndrome, identification of CMV within tissue on colon biopsies, and histologic changes consistent with CMV infection on a biopsy specimen. Colitis from CMV typically occurs when the CD4 count is less than 50 cells/mm^3.
- Diarrhea caused by MAC infection is usually associated with systemic symptoms, including weight loss. A person with disseminated MAC infection may present with acute symptoms, or presentation may be more subacute to chronic. The CD4 count is generally less than 50 cells/mm^3. The diagnosis is typically made by a positive AFB blood culture. Imaging of the abdomen by CT may demonstrate lymphadenopathy, hepatosplenomegaly, or small bowel thickening. A stool culture positive for MAC does not establish a diagnosis of MAC infection.
- The most common antiretrovirals to cause diarrhea are protease inhibitors and boosting agents (ritonavir and cobicistat).
- Acute hepatitis A infection should be considered in a person with diarrhea and fever or systemic symptoms, especially if they are homeless and have elevated alanine aminotransferase (ALT) or alanine aminotransferase (AST) levels.
- COVID-19 illness may be associated with GI symptoms, including diarrhea, in 10% or more of cases. If there is associated fever, respiratory symptoms, or known exposure, consider SARS-CoV-2 infection as a potential cause and perform respiratory PCR testing.

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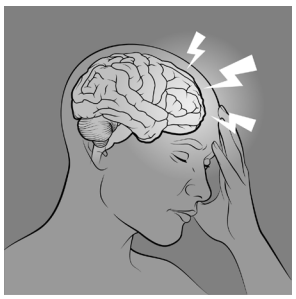

GUIDE NO. 4

Evaluation of Subacute Headache in Persons with HIV

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Gretchen Snoeyenbos Newman, MD[3] / Ronald D. Wilcox, MD[4] / David H. Spach, MD[1]

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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.

PERMISSIONS

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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/mm^3 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/mm^3, 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.

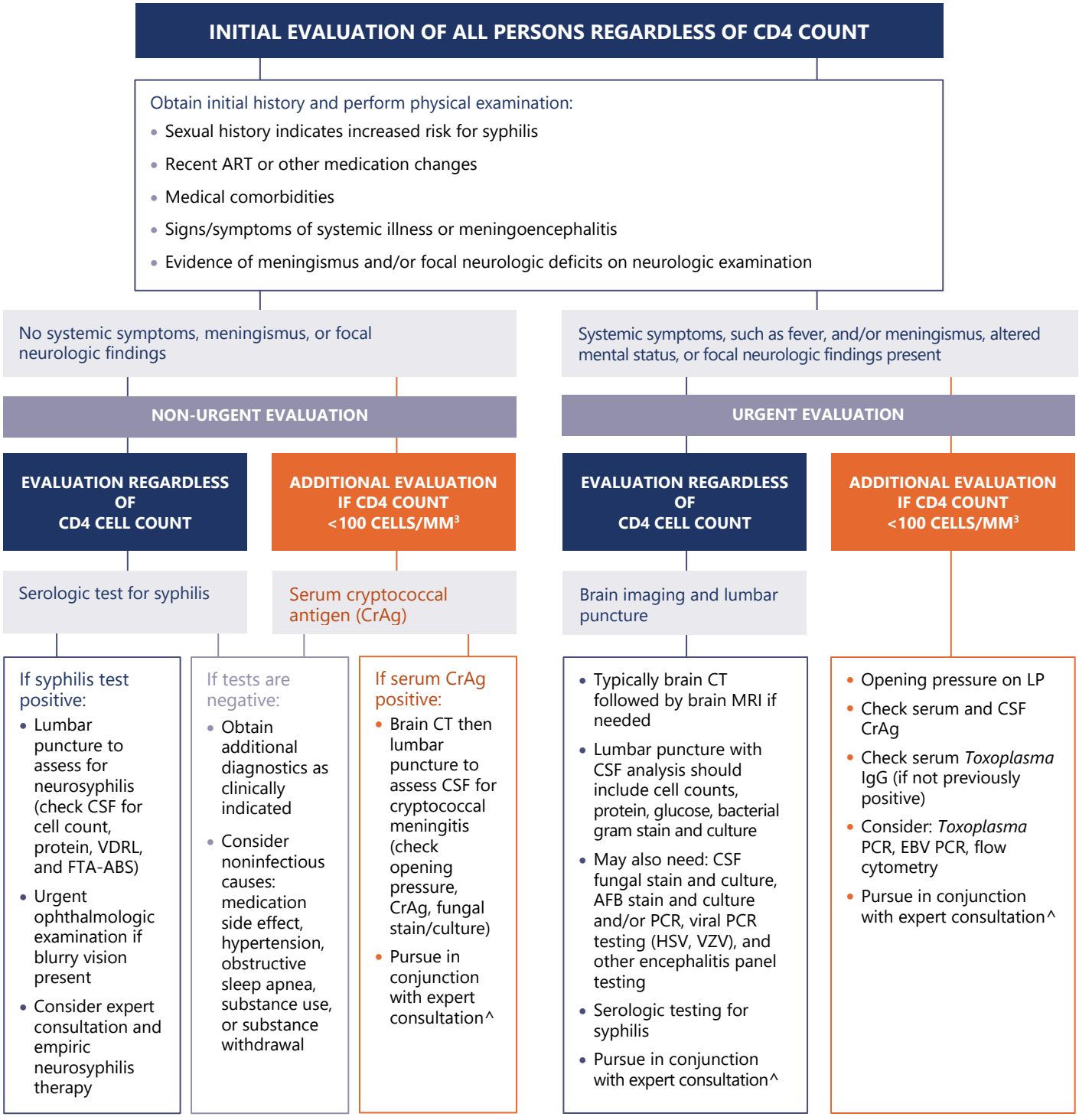
Does the individual have any underlying comorbidities or chronic medical conditions?

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).

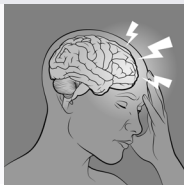
ABBREVIATIONS: AFB = acid fast bacilli; CSF = cerebrospinal fluid; CrAg = cryptococcal antigen; CSF = cerebrospinal fluid; CT = computed tomography; EBV = Epstein-Barr virus; FTA-ABS = fluorescent treponemal antibody absorbed; HSV = herpes simplex virus; LP = lumbar puncture; MRI = magnetic resonance 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
Toxoplasma encephalitis	Positive serum *Toxoplasma* IgG Seizures, altered mental status, focal deficits and/or fever	<100 cells/mm^3	MRI brain Serum *Toxoplasma* IgG CSF *Toxoplasma* 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/mm^3 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/mm^3, 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/mm^3 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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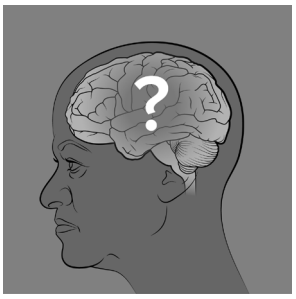

GUIDE NO. 5

Evaluation of Chronic Memory Changes in Persons with HIV

Gretchen Snoeyenbos Newman, MD[1] / Brian R. Wood, MD[2] / Jehan Z. Budak, MD[2] / Aley G. Kalapila, MD[3] / Ronald D. Wilcox, MD[4] / David H. Spach, MD[2]

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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 chronic memory changes 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.

PERMISSIONS

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DEFINITIONS OF ACUTE VERSUS CHRONIC MEMORY CHANGES

Chronic memory changes are those lasting months or longer. Such changes must be distinguished from acute mental status changes or neurologic deficits, which should prompt emergent evaluation.

KEY CLINICAL QUESTIONS

What is the most recent CD4 cell count?

Persons not taking antiretroviral therapy (ART) and with a low CD4 cell count are at increased risk for central nervous system opportunistic infections. Certain opportunistic infections may present with chronic memory changes, such as progressive multifocal leukoencephalopathy (PML), which typically occurs when the CD4 count is less than 50 cells/mm^3 but may occur at higher levels.

Is the person taking a medication known to cause neurologic or cognitive side effects?

In general, antiretroviral medications are unlikely to cause memory impairment, though the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz can cause insomnia, depression, and other neuropsychiatric symptoms, which may contribute to or worsen cognitive complaints. Non-antiretroviral medications, such as benzodiazepines, opiates, and other central nervous depressants, especially in the setting of polypharmacy, can impact cognition.

Has syphilis testing been performed?

Although persons with neurosyphilis are more likely to present with acute or subacute neurological symptoms (including ocular, auditory, or vestibular changes), subtle neurologic symptoms can occur, including long-term cognitive changes.

Are there associated symptoms that suggest a metabolic, toxic, or psychiatric disorder?

Particular attention should be paid to symptoms of thyroid disease, liver disease, vitamin deficiencies, depression, anxiety, and substance use, including alcohol and marijuana.

Are there signs or symptoms that suggest obstructive sleep apnea?

Obstructive sleep apnea is a common cause of memory impairment in persons with HIV, even with normal body mass index (BMI). Evaluation should be pursued, especially in the setting of concurrent fatigue, headaches, and/or hypertension.

Could HIV infection be the cause?

Cognitive impairment secondary to HIV itself includes a spectrum of disorders known as HIV-associated neurocognitive disorders (HAND), the most severe of which is called HIV-associated dementia (HAD). These are more likely if a person has longstanding HIV, is not taking ART, and/or has a low CD4 cell count nadir. Rarely, a person taking antiretroviral therapy (ART) may have continued HIV replication in the central nervous system (CNS) despite suppressed plasma HIV RNA levels; this condition is known as "CNS escape syndrome" and may contribute to cognitive impairment.

DIAGNOSTIC APPROACH TO CHRONIC MEMORY CHANGES IN PERSONS WITH HIV

INITIAL EVALUATION OF ALL PERSONS REGARDLESS OF CD4 COUNT OR ART STATUS

Obtain medical, psychiatric, and sexual history; review medication list; screen for substance use, and perform physical examination, including neurologic examination

Order laboratory tests, including complete metabolic panel, TSH, B12, folate, serologic testing for syphilis, hepatitis B and C testing

History, physical examination, and/or laboratory evaluation suggests metabolic, toxic, vascular, or psychiatric cause of memory changes

Treat identified cause of memory changes

No evidence of metabolic, toxic, vascular, or psychiatric causes of memory changes

MRI brain (with contrast if no contraindication)

Consider CSF evaluation (as indicated by clinical presentation and MRI findings, including evaluation for CNS infection, HIV CNS escape, and non-HIV-related processes)

Cause of memory changes identified

Treat identified cause of memory changes

No cause of memory change identified

Evaluate level of impairment using a validated tool for HAND and refer for formal neurocognitive testing

Asymptomatic neurocognitive impairment

Mild impairment in at least 2 domains not attributable to comorbid conditions AND not causing functional impairment

Mild neurocognitive disorder

Mild impairment in at least 2 domains not attributable to comorbid conditions AND functional impairment in ADLs

HIV-associated dementia

At least moderate impairment in at least 2 domains not attributable to comorbid conditions AND major functional impairment

ADDITIONAL EVALUATION IF CD4 COUNT <200 CELLS/MM^3

In addition to performing the recommended evaluation for persons with any CD4 cell count, add:

- MRI brain (with contrast if no contraindication)
- CSF evaluation (as indicated by clinical presentation and MRI findings, consider evaluation for PML, neurosyphilis, HIV CNS escape, and non-HIV-related causes)
- Evaluation is typically performed in conjunction with expert consultation^

^ 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).

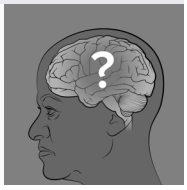
ABBREVIATIONS: ART = antiretroviral therapy; ADL = activities of daily living; CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; HAND = HIV-associated neurocognitive disorder; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy; TSH = thyroid stimulating hormone

COMMON CAUSES AND INITIAL DIAGNOSTIC EVALUATION FOR CHRONIC MEMORY CHANGES IN PERSONS WITH HIV

CAUSE (in alphabetical order)	RISK FACTORS AND CHARACTERISTICS	TYPICAL CD4 CELL COUNT	INITIAL DIAGNOSTIC EVALUATION
Brain tumor or brain metastases	May be associated with mood or personality change	Any	Brain imaging with CT or MRI, with contrast if no contraindication
HIV-associated neurocognitive disorder (HAND)/HIV-associated dementia (HAD)	Uncontrolled or longstanding controlled HIV Slowly progressive symptoms	Any; more prevalent with CD4 nadir <200 cells/mm^3	International HIV Dementia Scale (IHDS) https://www.hiv.uw.edu/page/mental-health-screening/ihds
HIV CNS escape syndrome	Good adherence to ART Cognitive symptoms not attributable to other causes	Any	CSF evaluation Detectable HIV RNA in CSF while undetectable in plasma
Major depression with cognitive dysfunction (pseudodementia)	Often accompanied by psychomotor slowing	Any	Validated depression screening tools and complete psychiatric evaluation
Metabolic disorder (thyroid disorders, vitamin B12 deficiency, etc.)	Poor nutrition History of thyroid disorders Concomitant physical examination signs	Any	CBC, CMP, thyroid studies, B12 level, and other tests as indicated
Neurosyphilis	Condomless sex History of untreated or incompletely treated syphilis	Any	Syphilis screening per local laboratory protocols CSF evaluation (cell counts, total protein, VDRL, and FTA-ABS)
Obstructive sleep apnea	Daily fatigue, chronic headaches, and/or HTN	Any	Overnight polysomnography
Progressive dementias (e.g., Alzheimer's, Lewy body, vascular, and others)	Gradual cognitive decline similar to course in person without HIV	Any	Evaluation similar to person without HIV Referral to neurologist for evaluation
Progressive multifocal leukoencephalopathy (PML)	Immunomodulatory humanized antibodies Uncontrolled HIV infection; receipt of immunomodulatory humanized antibodies	Usually <200 cells/mm^3	MRI brain with contrast (if no contraindication); MRI typically demonstrates multifocal white matter changes crossing the midline CSF evaluation (including JC virus PCR)
Substance use	May have waxing and waning quality	Any	Detailed history of current and prior drug use Drug screen as appropriate

ABBREVIATIONS: ART = antiretroviral therapy; CBC = complete blood counts; CMP = complete metabolic panel; CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; FTA-ABS = fluorescent treponemal antibody absorption; HTN = hypertension; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; RNA = ribonucleic acid; VDRL = venereal disease research laboratory

KEY SUMMARY POINTS



- In general, there is a 2-step approach to evaluating chronic memory changes in persons with HIV: (1) evaluate for an infectious, toxic, metabolic, or psychiatric process, and (2) if none are present, perform cognitive testing to confirm cognitive deficits, identify domains with limitations, and document extent of difficulties.
- Many factors that contribute to chronic memory impairment in persons with HIV are not directly related to HIV or ART. These include depression, anxiety, substance use, polypharmacy, insulin resistance, and obstructive sleep apnea.
- All persons with memory impairment or dementia symptoms should be screened for syphilis. Isolated memory or cognitive changes are rare manifestations of neurosyphilis.
- Consider performing MRI and CSF evaluation, particularly if the current or recent CD4 count is less than 200 cells/mm^3, other neurologic symptoms are present, or symptoms are progressive. The MRI is ideally performed with contrast and can evaluate for certain opportunistic infections (including PML) as well as non-HIV-related causes, such as primary brain tumor or metastases to the brain.
- Evaluation of the CSF may help identify opportunistic infections or other coinfections, such as neurosyphilis. In addition, HIV CNS escape syndrome (detection of HIV RNA in the CSF of a person on ART with an undetectable plasma HIV RNA) should be considered if other causes have been ruled out.
- Progressive dementias, such as Alzheimer's, Lewy body, and vascular, can occur at any CD4 cell count and should be considered when clinical signs and symptoms are compatible with no other cause of cognitive impairment identified.
- If deficits remain after toxic, metabolic, and infectious causes have been treated or excluded, a diagnosis of HAND should be considered. There are three HAND sub-types: asymptomatic neurocognitive impairment (ANI), which does not interfere with everyday functioning; mild neurocognitive disorder (MND), which leads to some interference with daily activities; and HIV-associated dementia (HAD), which causes marked impairment of function. Validated tools for assessing the likelihood of HAND exist (e.g., International HIV Dementia Scale).
- Formal neuropsychological testing by an experienced provider is useful for establishing the diagnosis of HAND and identifying areas of deficit. A person with HIV not yet taking ART should start soon; otherwise, currently, there is no specific medication to treat HAND. Cardiovascular exercise has been shown to help reduce symptoms. Identifying areas of deficit aids in designing personalized interventions to support adherence and activities of daily living.

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