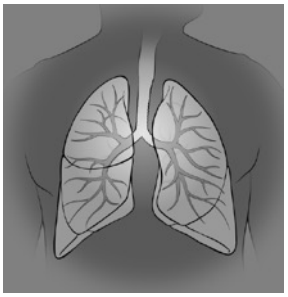

GUIDE NO. 1

Evaluation of Cough and Dyspnea 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 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 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

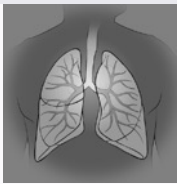
COMMON CAUSES AND INITIAL DIAGNOSTIC EVALUATION FOR ACUTE OR SUBACUTE COUGH AND/OR DYSPNEA IN PERSONS WITH HIV

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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