HIV-Associated Lung Disease

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Educational Objectives:

1. Develop a general approach to the HIV-positive outpatient presenting with pulmonary complaints.
2. Understand the changing epidemiology of classic AIDS-defining illnesses with pulmonary involvement in the antiretroviral therapy (ART) era.
3. Understand how HIV may impact the natural history and risk related to non-HIV-related pulmonary conditions.

Scenario:

A 49-year-old, HIV+ woman presents for evaluation of cough with abnormal chest imaging. She has a prior history of IV drug use and relays a history of HIV, diagnosed about 1 year ago by routine screening. At diagnosis, her CD4 count was 145 cells/mm^3; Quantiferon testing was negative. Her CXR at that time was normal. At diagnosis, she was initiated on a boosted protease inhibitor-based regimen (darunavir/ritonavir/tenofovir/emtricitabine), with eventual improvement in CD4 counts to >400.

Over the past 6 months, she has noted increased dry cough and mild-moderate dyspnea on exertion that is relatively constant, along with fatigue. She denies hemoptysis, fevers, sweats, headache, rash, GI complaints, or weight loss. She is a Philadelphia native without significant travel history.

She had childhood asthma, which was not active in early adulthood; she would take fluticasone-salmeterol intermittently when she felt like she needed it, but her prescription expired some years ago. She has an albuterol inhaler, which she has been taking more regularly over the past 6 months, and thinks that it may help. She has smoked ~1 ppd since her 20's.

She is afebrile, with S_aO_2 on RA = 94%. Her lung sounds are mildly diminished but otherwise clear. There is no wasting, rash, lymphadenopathy, or hepatosplenomegaly. A new CXR was obtained.

Question 1: How would you approach the differential diagnosis for this case?

Initial consideration of the degree of immunosuppression (i.e., CD4 count) is a reasonable place to start, and when cross-referenced with key symptoms and radiographic patterns, this approach can reliably narrow the differential.[1] Geographical location should also be a consideration as infectious diseases can vary significantly (e.g., TB is the most common pulmonary complication in HIV in Africa,[15] but in the developing world bacterial pneumonia is the most common infectious complication[16]).

CD4 Count	Respiratory Illness
Any	Acute bronchitis Bacterial pneumonia Pulmonary Embolism Bronchogenic carcinoma Lymphoma Sarcoidosis COPD Pulmonary Arterial Hypertension Nonspecific Interstitial Pneumonia
≤500	Recurrent bacterial pneumonia "Typical" pulmonary TB LIP (usually not <350)
≤200	*Pneumocystis jirovecii* pneumonia (PJP) Cryptococcal pneumonia "Atypical" pulmonary TB & possibly disseminated infection
≤100	Pulmonary Kaposi sarcoma Toxoplasma pneumonitis
≤50	Disseminated *Histoplasma* Disseminated *Coccidioides* *Aspergillus* pneumonia CMV pneumonia Disseminated MAI *Nocardia* *Rhodococcus* Lymphoma

Table above adapted from Tokman S, Huang L. Evaluation of respiratory disease. Clin Chest Med 2013.

The following tables summarize the differential diagnosis when considered from a radiographic standpoint:[2,3]

Consolidation	**Ground-Glass Opacity**	**Cysts**	**Peribronchovascular Opacities**
Infection Bacterial *If CD4 <200 cells/mm^3:* Mycobacterial Fungal	Infection Viral Atypical bacterial *If CD4 <200 cells/mm^3:* PJP *If CD4 <100 cells/mm^3*: CMV	Infection If CD4 <200 cells/mm^3, PJP	Neoplasm If CD4 <200 cells/mm^3, Kaposi sarcoma Lymphoma Lymphangitic carcinomatosis
Neoplasm Lymphoma Lung Cancer	Interstitial Lung Disease LIP NSIP	Interstitial Lung Disease LIP	Interstitial Lung Disease LIP Sarcoidosis

Table 1: Radiologic Findings and Associated Differential Diagnoses in Patients with HIV Infection. Adapted from Lichten berger JP et al. "What a Differential a Virus Makes: A Practical Approach to Thoracic Imaging Findings in the Context of HIV infection--Part 1, Pulmonary Findings," Am J of Roentgenology 2012; 198(6): 1295-304. Note: PJP = Pneumocystis jirovecii pneumonia; CMV = cytomegalovirus; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia.

Micronodules (<1 cm)	**Macronodules (>1 cm)**	**Cavitary Lesions**
Centrilobular ("tree-in-bud") Infectious Bacterial Viral *If CD4 <200 cells/mm^3:* Mycobacterial Fungal Non-infections LIP Perilymphatic Distribution Sarcoidosis LIP Lymphangitic carcinomatosis Miliary Distribution Infectious Tuberculosis NTM Fungal Toxoplasma Non-infectious Metastatic disease	Neoplasm Lymphoma Lung cancer Metastatic disease Infectious Mycobacterial Fungal Septic emboli	Infectious Bacterial pneumonia Bacterial abscess Mycobacterial Fungal Septic emboli Non-infectious Necrotic carcinoma Lymphoma

Table 2: Features of Pulmonary Nodules and the Associated Differential Diagnoses in Patients with HIV Infection. Adapted from Lichten berger JP et al. "What a Differential a Virus Makes: A Practical Approach to Thoracic Imaging Findings in the Context of HIV infection--Part 1, Pulmonary Findings," Am J of Roentgenology 2012; 198(6): 1295-304. Note: PJP = Pneumocystis jirovecii pneumonia; NTM = nontuberculous mycobacterium; LIP = lymphocytic interstitial pneumonia.

Endemic mycoses (Histoplasmosis, Blastomycosis, Coccidioidomycosis) will need to be considered based on local risk and prevalence or relevant travel history. Clinical and imaging findings will offer valuable information and can be supplemented by laboratory tests. Various antigen tests (Cryptococcal antigen, Urine Histoplasma antigen, Blastomyces antigen) in the right clinical context can be a simple starting point to evaluate suspected infection by endemic mycoses. High levels of blood beta-D-glucan have demonstrated a correlation with HIV-related PJP, although the precise role of this test remains to be defined[17].

Question 2: Could this be an immune reconstitution phenomenon?

Possibly. IRIS (immune reconstitution inflammatory syndrome) can occur in the context of multiple infections, including M.Tb and NTM, PJP, and Cryptococcus, as well as non-infectious conditions like Kaposi's sarcoma. The timing of the onset of symptoms can be helpful; in one prospective study, the median onset of IRIS was 48 days (IQR 29-99 days).[4] Fever is typical, and neurologic symptoms are common, particularly with cryptococcus and M.Tb. The combination of neurologic symptoms and abnormal chest imaging should prompt a directed evaluation for mycobacterial or fungal pathogens, including CSF analysis. When endemic mycoses present with pneumonia in HIV, it is usually in the context of disseminated disease. Lymphadenopathy with a *low-attenuation center* strongly suggests an infectious etiology (mycobacterial or fungal).[3]

However, in this case, the onset of symptoms (~6 months after ART initiation) is a bit long, and the initial CD4 count in IRIS tends to be lower than this patient's (often <100 cells/mm^3, though preexisting M.Tb infection is an exception). This, along with the lack of fever, make traditional IRIS unlikely in this patient.

Question 3: How helpful is the Quantiferon test?

Interferon-gamma release assays (IGRAs) appear to have similar (imperfect) sensitivity compared with tuberculin skin testing (60-70%) for identifying M.tb infection; the T-SPOT TB assay may be slightly more sensitive.[5] If the initial test was done with a CD4 count <200 cells/mm^3, some recommend repeating the test once the count surpasses this threshold on therapy.

Question 4: What non-infectious processes should be considered?

Malignancy[6] **Kaposi sarcoma (KS)** and **non-Hodgkin lymphoma (NHL)** are two classic AIDS-defining malignancies; however, their incidence has declined in the ART area, corroborating a link between risk and level of immunosuppression. **KS** occurs largely in men who have sex with men and at very low CD4 counts. CT findings include peribronchovascular nodularity & thickening (classically, in a "flame" shape), interlobular septal thickening, and fissure nodularity; adenopathy can also be seen (Figure 1). The parenchymal abnormalities tend to have a *lower-lobe predominance*, and lymph nodes may *enhance*. Pulmonary disease can exist in the absence of cutaneous disease.

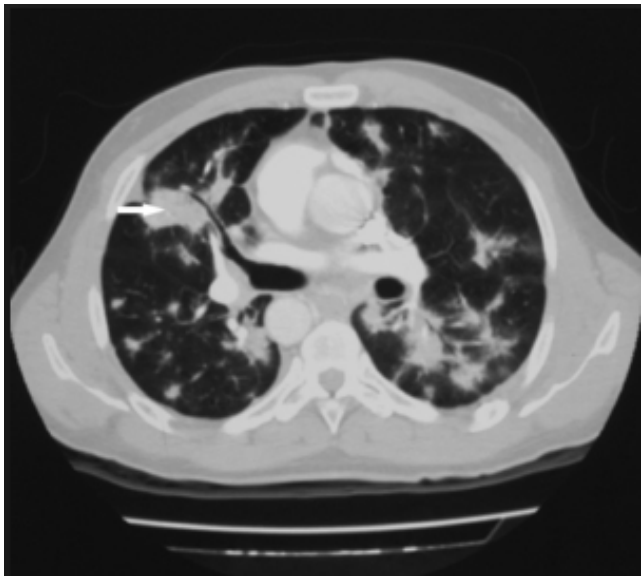

Figure 1: Kaposi's sarcoma – peribronchovascular flame-shaped densities (noted by white arrow).

The incidence of **NHL** has decreased in the ART era. However, the link with a low CD4 count is perhaps less clear than with KS; thus, a relatively preserved CD4 count cannot rule out the possibility of lymphoma. Most HIV-related NHL is of the diffuse large B-cell type, many of which are associated with EBV infection. While not a likely consideration for this patent, primary effusion lymphoma is a rare type of NHL that is associated with HIV infection and can present in the pleural or pericardial space but also the peritoneum[6].

Multicentric Castleman disease (MCD) has been reported in HIV. About 50% of HIV-associated cases will have mediastinal adenopathy (much rarer in non-HIV MCD). MCD is also associated with a LIP-like pattern of the lung parenchyma. Like KS, adenopathy here may enhance, which is atypical for infectious processes. Peripheral lymphadenopathy and splenomegaly are the virtual rules, and fever is nearly universal. Our patient lacks these features[7].

Lymphocytic interstitial pneumonia (LIP) is the "classic" ILD associated with HIV infection, but it has been described most frequently in infants and children. Interestingly, LIP tends to be seen with higher CD4 counts, suggesting that a certain level of immune competency is required to drive the lymphocytic infiltration that characterizes the disease. HRCT findings include scattered ground glass opacities, nodules, and possibly cysts, often in a predominant lower-lobe distribution (Figure 2). This remains a possibility in our case; however, bulky adenopathy is not expected.

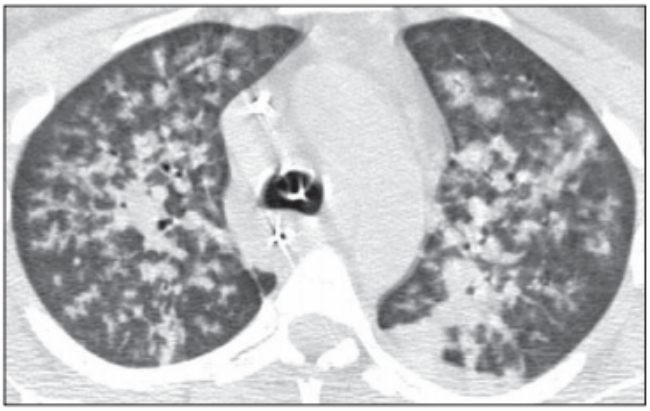

Figure 2: LIP –peribronchovascular nodules are present (typically <5mm); cysts are absent in this case.

Non-specific interstitial pneumonitis (NSIP) was described frequently in the pre-ART era, though the definition of the disease has evolved over the years. The appearance of NSIP in HIV is similar to non-HIV patients. It also tends to occur with higher CD4 counts, though lower than that seen in LIP; however, there is a wide overlap.

Sarcoidosis involved abnormalities in cell-mediated immunity and had been regarded as rare in HIV in the pre-ART era; however, there is a "resurgence" of this diagnosis, potentially related to ART-induced restoration of CD4-related immunity allowing the disease to manifest in susceptible patients.

☞ *Never forget about PJP as a cause of a sub-acute pulmonary presentation – this can cause a variety of CT patterns, many of which overlap with the above entities. The risk of PJP increases in patients with CD4 counts <200 cells/mm^3, especially in the absence of adequate prophylaxis.*

Scenario continued:

You obtain a high-resolution chest CT and PFTs. The chest CT confirms the CXR findings, including bilateral hilar adenopathy with mid- & upper zone-predominant micronodular interstitial changes in a bronchovascular distribution. There is no significant ground glass or cystic changes; however, mild upper-lobe centrilobular emphysema is apparent.

PFTs demonstrate a mixed obstructive-restrictive pattern, with an FEV1 of 65% predicted, no bronchodilator reversibility, and DLco 55% predicted.

Given the clinical context, sarcoidosis becomes the leading differential diagnostic consideration. You discuss proceeding with bronchoscopy, and the patient agrees. She asks if anything can be done to make her feel better.

Question 5: Based on your information, should you put her on other inhalers?

The PFTs suggest an element of obstruction without bronchodilator reversibility, and the CT reveals emphysema in addition to the interstitial changes.

It is now fairly well-established that HIV infection predisposes patients to premature emphysema.[8] In one study, 23% of HIV-infected smokers (without a history of pulmonary infections) demonstrated emphysema by either PFTs or CT scans compared with 2% of HIV-uninfected controls matched for age and smoking history.[9] COPD can also present at an earlier age, and may be more likely to experience acute exacerbations of COPD[18]. Multiple cohorts have suggested a 15-20% prevalence of airway obstruction using typical spirometric criteria; associated factors include age, smoking, IV drug use, and history of PJP pneumonia. A longitudinal study of HIV+ individuals with substance use disorder found that higher viral loads or lower CD4 counts (<100) were associated with a greater decline in FEV1 and FVC over time; the rate of decline in those with well-controlled HIV was similar to that of HIV-uninfected patients.[10]

The link between HIV and asthma is perhaps less well-established. Still, in one study, 21% of HIV-infected persons carried a self-reported asthma diagnosis, compared with ~9% in the general population.[11]

Given the CT and PFT findings, initiating long-acting bronchodilator therapy would be reasonable (e.g., LAMA +/- LABA).[19] There are no HIV-specific guidelines, so treatment generally mirrors the approach used in non-HIV patients. Drug-drug interactions should always be kept in mind; a particular concern is the boosting effect of protease inhibitors on fluticasone, which can lead to frank Cushing syndrome or adrenal insufficiency.

Smoking cessation should always be recommended, especially in patients with HIV. A national cohort study suggested that the attributable risk of smoking-related death in HIV patients is double that of uninfected persons. HIV-infected smokers lose more life years to smoking than to HIV infection.[12] Both behavioral and pharmacologic methods of smoking cessation are effective in patients with HIV, similar to other smokers. Varenicline is effective for smoking cessation and well tolerated in patients with HIV.[20]

Scenario continued:

You start the patient on inhaled tiotropium and she undergoes bronchoscopy**.**

The airways appear mildly inflamed. Transbronchial biopsies reveal non-caseating granulomas, with negative special stains/cytology and negative cultures from a BAL – consistent with a final diagnosis of sarcoidosis.

Given the symptoms and PFT impairment, you initiate the patient on prednisone at ~0.5 mg/kg/day.

The patient is lost to follow-up for a period but returns 4 months later. Her breathing and cough have improved, but now she displays Cushingoid features.

Repeat PFTs show improved FEV1 and FVC. A repeat CT chest shows improved peri-bronchovascular nodularity but a new 8mm ground glass nodule in the RUL. You begin to wean her steroids and plan for follow-up imaging.

Question 6: What is the impact of HIV infection on the epidemiology of lung cancer?

The incidence of AIDS-defining malignancies (Kaposi sarcoma and non-Hodgkin's lymphoma) has decreased in the ART era. However, the incidence of other cancers, including lung, has increased (Figure 3):[13]

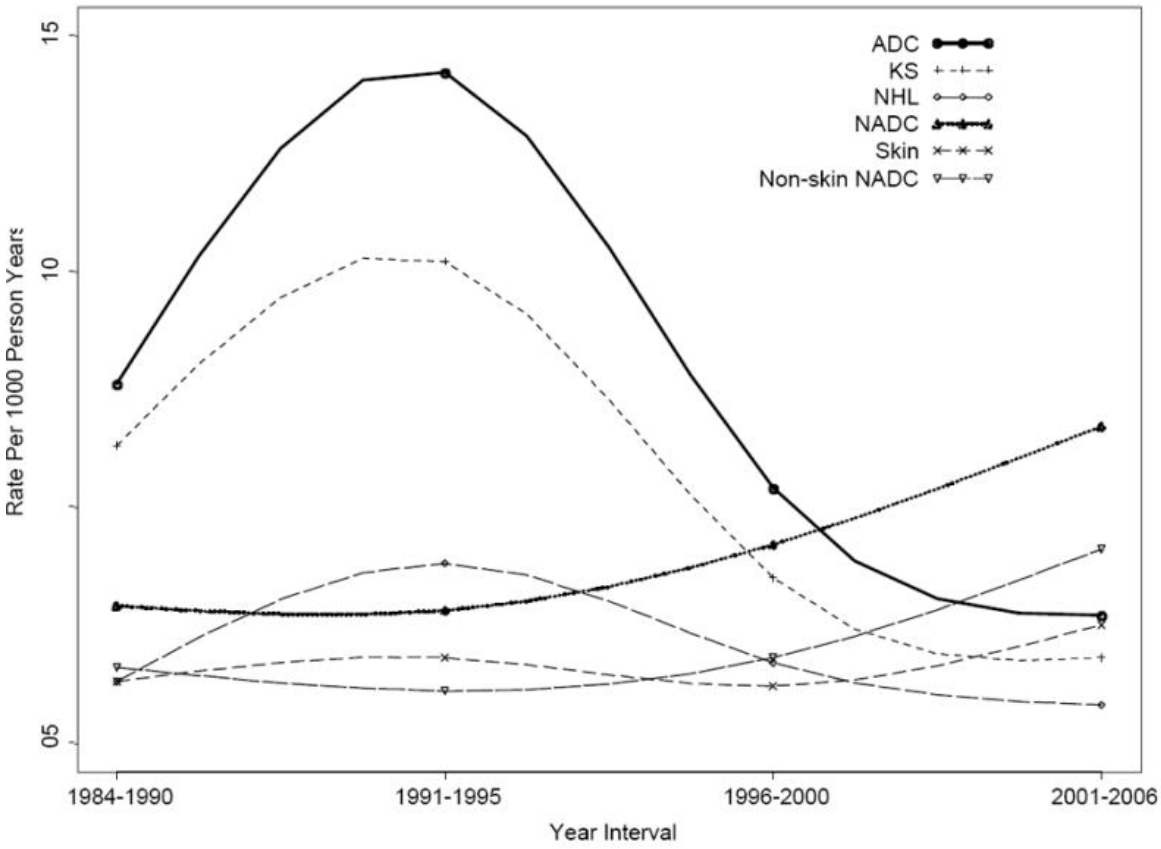

Figure 3: Cancer Incidence Over Time in Patients with HIV Infection. This figure (from Crum-Cianflone N, et al. "Trends in the Incidence of Cancers among HIV-Infected Persons and the Impact of Antiretroviral Therapy: A 20-Year Cohort Study," AIDS 2009; 23(1): 41-50) illustrates the changes over time in types of cancers prevalent in patients with HIV infection. ADC = AIDS defining cancer; KS = Kaposi sarcoma; NHL = non-Hodgkin's lymphoma; NADC = non-AIDS defining cancer.

While it is true that smoking prevalence is higher among the HIV-infected population, similar to the COPD population, the presence of HIV infection appears to independently increase the risk of developing lung cancer (2 to 4-fold increased risk) after adjusting for tobacco use. Low CD4+counts and prior pneumonia are associated with increased lung cancer risk[21]. Cigarette smoke, HIV infection, and chronic inflammation can increase oxidative stress, leading to oxidative DNA damage. This has been postulated as a possible mechanism for increased cancer risk in people living with HIV. Early initiation of antiretroviral therapy has been associated with reduced risk of lung cancer in this population[22].

There are limited data on lung cancer screening for people living with HIV, given that patients with HIV were not included in the NLST. The American Thoracic Society has advocated for more research to determine whether lung cancer screening for people with HIV who do not have tobacco exposure is warranted[23]. For patients with a sufficient smoking history, standard lung cancer screening criteria should be applied, and the presence of HIV as an independent risk factor should be discussed when counseling patients on the risks/benefits of screening. Additionally, it should be noted that there will likely be a higher percentage of incidental findings in this population than in patients without HIV.

Question 7: The patient mentions that she has read online that HIV is a risk factor for pulmonary hypertension. What is this patient's risk of developing pulmonary arterial hypertension? How does ART impact this risk?

PAH has an incidence of 0.5% in HIV. PAH occurring in HIV[14] appears histologically identical to idiopathic PAH, placing it within Group 1 of the World Health Organization classification system. There has been no consistent association with CD4 count, which suggests that the level of immune suppression (or treatment thereof) does not modify the risk of PAH. Risk factors associated with the development of PAH include female sex, IV drug use, detectable HIV viremia, and co-existing HCV infection.

While the live virus has never been shown to infect pulmonary vascular cells, HIV proteins have been isolated from endothelial cells of HIV patients with PAH. Interestingly these proteins have been shown *in vivo* to adversely influence signaling within BMPR2 (TGF-β superfamily), HIF-1α, and endothelin pathways – all of which are implicated in the pathogenesis of PAH in general.

The presentation of PAH in HIV and the diagnostic approach is similar to other forms of PAH. Patients with HIV are vastly under-represented (or absent) from the pivotal trials of available PAH agents. Drug-drug interactions are important to consider; protease-inhibitors can boost the serum concentrations of some ERAs (endothelin receptor antagonists) and PDE5 inhibitors. Of the available oral agents, no interactions exist with the new prostacyclin derivatives (oral treprostinil and selexipag). Ambrisentan is the ERA with the fewest interactions. Both PDE5-Is (though perhaps less with tadalafil) and riociguat require close follow-up due to these boosting effects.

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Pre/Post-Test Questions:

1. A 36-year-old woman presents to your clinic with worsening dyspnea over the last 2-3 months. She was diagnosed with HIV two years ago. She intermittently complies with ART; the most recent CD4 count was 156 cells/mm^3. She reports a low-grade fever (Tm 99-100°C) in the last week and a cough productive of white-yellow sputum. She has not had any recent travel and denies any sick contacts. She is a non-smoker. She has been lost to follow-up from her infectious disease doctor and is only intermittently taking her prescribed medications. She is not currently taking any antibiotics for prophylaxis. Given her symptoms, you are concerned about an infectious process and order a chest CT. She has no prior imaging in the system or PFTs. While awaiting the CT scan results, which of the following would you consider as diagnostic possibilities for this patient's condition based on her CD4 count?
    a. CMV
    b. Aspergillus pneumonia
    c. PJP Pneumonia
    d. Bacterial Pneumonia
    e. Any of the above
    f. C&D

2. A 55-year-old man with a history of well-controlled HIV (CD 400 cells/mm^3, viral load undetectable) and COPD comes to your office for a routine follow-up. Reviewing his medication list, you note that he is on ART, including a protease inhibitor. To date, he has been maintained on albuterol as needed alone for the management of his COPD, but he notes that he feels that his symptoms have been worse in the last 6 months. You are considering starting him on a long-acting inhaler to help improve his symptom management. Which of the following inhalers should be avoided in this patient?
    a. Tiotropium
    b. Formoterol
    c. Fluticasone
    d. All are safe
    e. All should be avoided in this patient

3. A 35-year-old woman with a history of well-controlled HIV (CD4 480 cells/mm^3, undetectable viral load) and HCV comes to your office to evaluate progressive dyspnea. She had a chest CT with no parenchymal abnormalities. Her PFTs were notable for normal spirometry. DLCO was not performed. You are considering possible etiologies for her dyspnea and the possibility of pulmonary hypertension (PH). Which of the following statements is true regarding pulmonary hypertension in this patient?
    a. PH is common in HIV-infected patients and thus is a likely culprit of her dyspnea.
    b. Because her HIV is well-controlled, her risk for HIV-associated PH is reduced.
    c. Her history of HCV is an additional risk factor for HIV-associated PH
    d. All of the above
    e. None of the above