Human Immunodeficiency Virus (HIV) Infection and AIDS

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BAL	Bronchoalveolar lavage
CCR5	Chemokine receptor type 5
CD4	Cluster of differentiation 4
CDC	Centers for disease control and prevention
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
DHHS	The United States Department of Health and Human Services
EBV	Epstein–Barr virus
FDA	The United States Food and Drug Administration
GALT	Gut-associated lymphoid tissue
HIV	Human immunodeficiency virus
HPTN	The HIV prevention trials network
IFNγ	Interferon gamma
INSTI	Integrase strand transfer inhibitor
KS	Kaposi sarcoma
LDH	Lactate dehydrogenase
MAC	*Mycobacterium avium* complex
MSM	Men who have sex with men
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside (nucleotide) reverse transcriptase inhibitors
PAS	Periodic acid–Schiff
PCP	*Pneumocystis jirovecii* pneumonia
PCR	Polymerase chain reaction
PPD	Purified protein derivative
PrEP	Preexposure prophylaxis
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
STI	Sexually transmitted infection
TB	Tuberculosis
TMP-SMX	Trimethoprim-Sulfamethoxazole
U=U	Undetectable = Untransmissible
WHO	The World Health Organization

Case 1

A 45-year-old woman presents to her family physician's office complaining of fever, sore throat, and a rash. She was seen 1 week ago in the emergency room where she tested negative for mononucleosis and streptococcal pharyngitis and was given a diagnosis of viral syndrome. Her last negative HIV test was during her last full-term pregnancy, 15 years ago. She has not been sexually active until very recently; 3 weeks ago she had unprotected vaginal sex with a new partner.

Question 1

What symptom is NOT part of the acute retroviral syndrome?

A. Morbilliform rash
B. Pharyngitis
C. Dyspnea
D. Cervical lymphadenopathy
E. Fever

Answer and Explanation

Answer: C

The differential diagnosis for this patient should include all etiologies of mononucleosis like syndrome, including HIV. Dyspnea is not characteristic for this syndrome, while all other listed symptoms are present in >80% of symptomatic acute HIV.

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1 HIV Epidemiology, Transmission, and Natural History

CDC estimates that, in 2019, approximately 1.2 million persons with HIV lived in United States, out of which circa 160,000 were undiagnosed, a segment that not only does not take advantage of treatment, but also is more likely to contribute to new infections. While the HIV incidence has been decreasing in US, the prevalence continues to increase, as the number of new infections outpaces the number of deaths. The infection disproportionately affects particular racial, sex, and age groups, with 78% of infected persons being male and 42% Black/African American (which constitute only 13% of the US population). The largest number of new diagnoses occurs in persons aged 20–34, but overall, the HIV population is aging, with almost two thirds being over 45 years old. Male to male sexual contact remains the most important method of transmission in US, as opposed to heterosexual sex and vertical transmission which are the drivers of the epidemic in sub-Saharan Africa. Vertical and postnatal mother to child transmission was not completely eliminated in the US, however universal opt-out screening during pregnancy, prenatal care, early or even pre-conception antiretroviral treatment and breastfeeding avoidance have significantly reduced the risk of HIV acquisition in infancy. Blood and blood products transmission in healthcare setting was virtually eliminated by screening in high-income countries including US but is still an ongoing threat in the developing world. Transmission through injection drug use remains an unsolved problem despite needle exchange programs and preexposure prophylaxis. Risk of HIV acquisition increases with the number of persons the index shares needles with. Saliva, sweat, tears, and urine were not shown to transmit HIV, even though the virus can be occasionally detected in low titers in these fluids.

The pathogenesis of acute HIV infection was well described in a simian model of genital mucosa acquisition, where tissue dendritic cells and macrophages act as targets for a single virion and then carriers to the lymphoid tissue. The CD4 receptor and the CCR5 coreceptor present on the surface of T cells and macrophages are essential in transmission of the virus and subsequent replication. A specific mutation to the CCR5, namely a 32-base deletion (CC5Δ32) leads to resistance to HIV infection.

Acute symptoms develop within 2–4 weeks of infection and while a number of infections can be asymptomatic, some individuals experience a nonspecific syndrome with fever, lymphadenopathy (cervical), a morbilliform rash, pharyngitis, and fatigue, rare manifestations including aseptic meningitis, Guillain-Barre syndrome or oral candidiasis are described. Viral infections including mononucleosis (acute infection with Epstein–Barr virus), acute cytomegalovirus, influenza, enterovirus, as well as other infections—toxoplasmosis, streptococcal pharyngitis, and syphilis can present in a similar manner and are part of the differential diagnosis. At this stage, a high HIV viral load would be detectable in the peripheral blood and most individuals have a positive p24 antigen. The presence of this very high viral load increases the likelihood of transmission, thus making recognition of this syndrome, linkage to care and early treatment even more important.

Early in the infection also the gastrointestinal system is an important target for the virus, one in five GALT T cells are infected in the acute HIV phase and most of them are lysed. The acute retroviral syndrome is followed by a period of viral latency (Fig. 1) associated with chronic infection, during which most individuals are asymptomatic. This period is characterized by a slow decline in the CD4+ T cell count over a period of 7–10 years. The attack on the mucosal lymphoid system continues and eventually leads to depletion of T cells in the intestinal mucosa. Rapid progression to AIDS is described to occur much earlier in individuals with a higher plasma viral load (over 100,000 copies/mL) at 6 months post-initial infection, when a setpoint is achieved. A lower T cell count at the set point is also associated with more rapid progression. Viral containment and the drop in the initial high viral load depend on anti-HIV CD8+ T cells. Throughout the chronic phase, the HIV infection elicits a significant activation of the immune response and the virus continues to evade it due to its ability to mutate frequently, related to the high rate of replication and the error prone transcription.

In late stages, the immune system collapses, which allows for very high viral loads to be detected again once a CD4+ T cell count reaches 200 cells/μL. This is a time when patients are at an increased risk for opportunistic infections and AIDS-defining malignancies.

Question 2

What is the test of choice for screening for HIV in this case?

A. HIV Western Blot
B. Combination antibody/antigen assay, followed by a differentiation assay
C. An over-the-counter home HIV test kit
D. CD4+ T cell count
E. HIV antibody ELISA

Answer and Explanation

Answer: B

All the above assays can be used for the diagnosis of HIV, however since 2014 the CDC recommends a combination antibody/antigen as the test of choice. Historically, the HIV ELISA was used for screening, and the confirmation was done with a cumbersome and time-consuming Western Blot. In 2010, FDA approved a test which included not only detection of HIV-1/2 antibodies, but also the p24 HIV-1 antigen. This test reduces the window period (between the acquisition of HIV and the time when a test would accurately detect infection) to as low as 2 weeks, although the CDC considers the window period to be 45 days, the time when the test becomes close to 100% sensitive. While the combination test does not require confirmation by Western

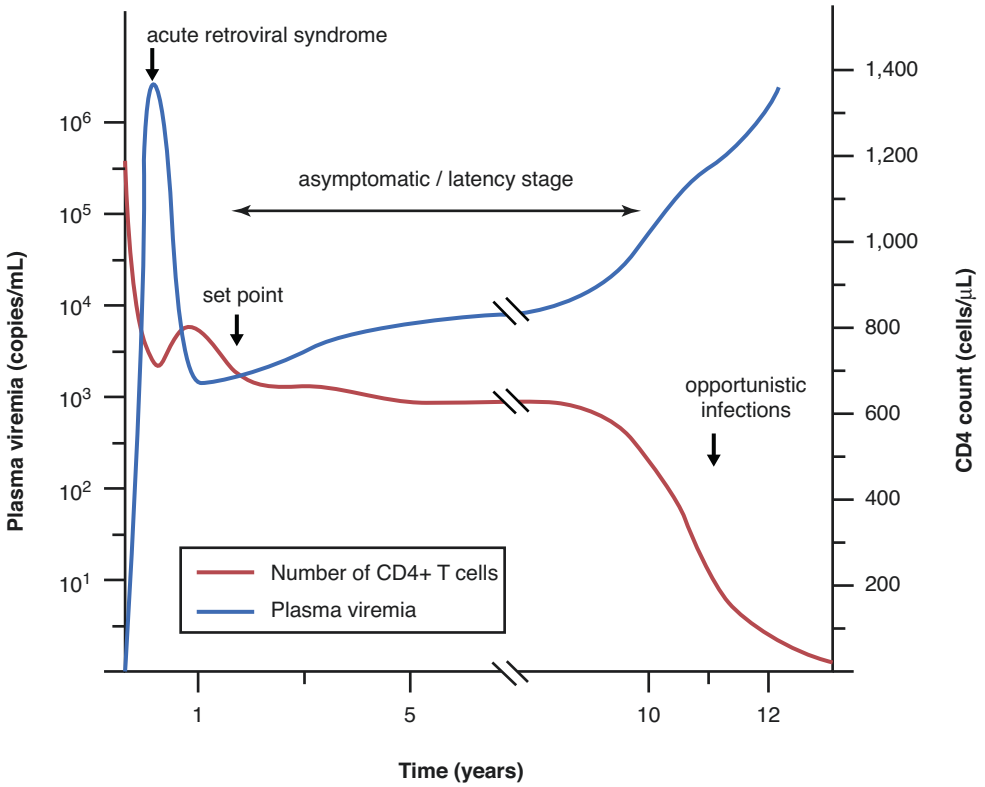

Fig. 1 Natural history of HIV infection in the absence of antiretroviral treatment. (Modified with permission from Gillespie S et al. Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome, in Clinical Immunology: Principles and Practice, 5th ed., 2019, 39, 545–560.e1 [1])

Blot, it cannot distinguish between HIV-1 and HIV-2 and when positive, must be followed by an immunochromatographic differentiation assay which both confirms the HIV infection and differentiates between HIV-1 and HIV-2. A qualitative HIV-1 DNA test can also be used, but it is not as widely available, is more expensive, and does not detect HIV-2. The HIV-1 RNA quantitative tests are widely available and are occasionally used off-label for diagnosis of acute retroviral syndrome, however, they were designed to be used for monitoring treatment, rather than for diagnosis, as false positive low-level amplification can occur. Also, the quantitative molecular test can be false negative in elite controllers (persons who, despite HIV infection, have no detectable viral load in the peripheral blood in the absence of antiretroviral treatment). The over-the-counter HIV tests are convenient and offer convenient in-home testing, however, when positive, they must be confirmed with a laboratory test. Counselling and linkage to care may also not be as robust with over-the-counter kits, as patients carry the burden to actively seek care, as opposed to being offered support at the time of being informed of a positive result in the case of laboratory tests.

2 HIV Screening and Diagnosis

The diagnosis of HIV is made with serological tests but can also be done with molecular tests. A low CD4+ T cell count should not be used for screening or diagnosis, as a multitude of conditions including acute viral illnesses, malignancies, and drugs can lead to such finding.

Table 1 HIV screening

Category of individuals	Screening frequency
All individuals 13–63 of age	Once, in all health care settings
High risk individuals • Sex partners of persons with HIV • Persons who inject drugs and their sex partners • Persons who have more than one sex partner since their last HIV test • Persons who exchange money for sex or drugs	Once a year
Pregnant women	Universal opt-out screening as early as possible in pregnancy; if high risk exposure, repeat test before week 36

HIV screening is crucial in detecting asymptomatic infections and since 2006 the CDC has recommended performing HIV screening for all persons 13–64 years of age in all health care settings. Screening refers to testing in the absence of symptoms suggestive of HIV infection (Table 1).

HIV testing does not require written consent, which was demonstrated to be a barrier to HIV testing. Even though the recommendations were issued in 2006, it took until 2018 for all states to pass legislation that was consistent with this recommendation. In the case of pregnant women, the test is universally offered but pregnant women still have the right to

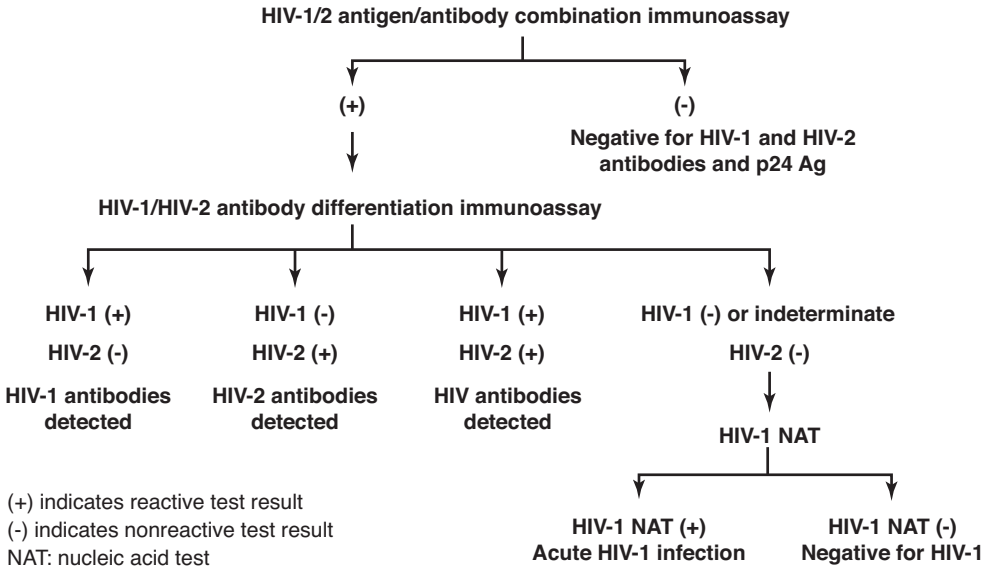

Fig. 2 The CDC recommended algorithm for HIV testing. (From the CDC: Quick Reference Guide—Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations June 27, 2014, public domain [2])

specifically decline it; providers should discuss and address the reasons behind refusal. Also, all individuals have the right to anonymous testing.

Delivering the test results can be done without direct contact between a provider and the patient, in the case of a negative HIV test. A positive test should be delivered by a person who can provide counselling; linkage to care at the time of diagnosis is crucial in assuring proper and timely further testing and treatment.

HIV infection stigma still represents a barrier to testing among patients and providers and it may be compounded by competing priorities, language, educational, and logistical barriers (Fig. 2).

The HIV NAT is a qualitative test FDA approved for diagnosis of HIV and is used when an infected individual is tested in the first few weeks after exposure, at a time when the HIV antibodies have not developed. The test can be obtained either after a combination assay was negative in a high-risk individual with clinical suspicion of acute retroviral syndrome or when a combination assay was positive, but the differentiation test is either negative or indeterminate (in this situation only the p24 antigen is positive and antibodies have not developed yet). NAT tests are also useful in evaluating neonates for vertical transmission, where maternal antibodies are present in the newborn's bloodstream.

The combination test reliably detects 99% of infections at 45 days after exposure, however more than half of infected individuals will have a positive test as early as 2 weeks into infection. HIV NAT tests become positive at approximately 7–10 days from infection. Antibody tests start being positive around 3–4 weeks. The now obsolete Western Blot was the last to become positive, starting at 6 weeks, and in some rare situations the test became fully positive as late as 6 months. Over the counter antibody assays are less sensitive than laboratory-based tests but offer the convenience and privacy of in-home testing; while the kit includes clear instructions and access to a confidential support center, the disadvantage is that the test needs to be confirmed by a laboratory test and individuals who tested positive may not seek care immediately.

Once linked to care, initial laboratory assessment includes HIV RNA viral load, CD4+ T cell count, HIV resistance testing, basic chemistry including fasting glucose, liver function tests and fasting lipid profile, CBC with differential, chlamydia, and gonorrhea genital, rectal or urine NAT, syphilis, hepatitis A, B, and C, as well as toxoplasma serology and cryptococcal antigen, latent tuberculosis screening either by skin testing or by an interferon gamma assay; serology for dimorphic fungal infections is recommended depending on geographic location and endemicity in the area. At the initial evaluation, a physical exam and a mini-mental status examination are performed and counselling regarding natural history and transmission should be done, pneumococcal, meningococcal, and hepatitis A and B immunizations should be considered and offered.

Question 3

Patient is diagnosed with HIV-1 infection based on positive serology. Her CD4+ T cell count is 620 cells/μL. She is presenting for her first clinic visit. She is not symptomatic at this point. What is the treatment recommendation?

A. Monitor CD4+ T cell count every 6 months and initiate antiretrovirals when it drops below 500
B. Monitor CD4+ T cell count every 3 months and initiate antiretrovirals when it drops below 300
C. Initiate antiretroviral treatment only if she develops opportunistic infections

D. Initiate antiretroviral treatment immediately and continue lifelong
E. Start combination three-drug combination antiretroviral treatment but stop if HIV viral load remains undetectable for at least 6 months

Answer and Explanation

Answer: D

The treatment recommendations have changed over the years. In the 1980s when the treatment options were very limited and side effects were significant, treatment was offered only for patients with advanced disease. As more options became available, the threshold for initiating antiretrovirals and the specific regimens used have drastically changed. The current recommendation is to initiate treatment as early as possible, irrespective of the T cell count or viral load, with very few exceptions (see below opportunistic infections). In addition, multiple studies demonstrated that interruptions in treatment—"drug holidays"—lead to opportunistic infections and cardiac events, resulting in poor outcomes and should not be offered. At this point, in the absence of a viable cure, the treatment is lifelong.

3 HIV Treatment Principles

Even though treatment of HIV is beyond the scope of this chapter, it is useful to be aware of the main principles that guide HIV management. Early initiation of HIV treatment starting with the first clinic visit leads indubitably to better outcomes not only to the patient but also impacts transmission. Uncontrolled HIV replication leads to perpetual activation of the immune system leading to a constant state of inflammation. Untreated persons who live with HIV have a higher risk of not only acquiring opportunistic infections and malignancy once the CD4T cell count drops below 200 cells/μL, but HIV affects almost every organ system: HIV nephropathy (1 in 5 untreated patients have microalbuminuria), diseases of cardiovascular system (coronary artery disease is much more common than in the HIV uninfected population and HIV cardiomyopathy—while not as common and usually associated with advanced disease, leads to congestive heart failure), metabolic and endocrine disorders (hypogonadism affects up to half of infected men, subclinical hypothyroidism, and even SIADH can be seen in advanced disease).

Transmission by sexual contact is eliminated in patients with undetectable HIV viral loads as demonstrated by large cohorts of both heterosexual (HPTN 052 trial) and male-male discordant couples (PARTNER and Opposites Attract trials) followed over extended periods of time. These findings led to the WHO recommendations and to changes in the DHHS guidelines which state now that all persons with HIV should be offered antiretroviral treatment.

An effective treatment consists of combinations that usually include three active drugs from at least two different classes, although in some specific situations two drug combinations can be used (patients who switch from certain stable regimens for regimen simplification, or who have low viral loads at the time of initiating treatment). Single drug regimens are highly discouraged as they rarely lead to sustained viral suppression.

When choosing an ART regimen, one must consider a multitude of factors, including preexistent chronic kidney disease, baseline cardiovascular risk and family history of coronary artery disease, age and reproductive status in women, pill burden, interactions, lifestyle, and even weight. Choosing the right regimen for each patient can have a huge impact on the long-term outcomes, due to potential side effects and multifactorial determinants of adherence.

Interruptions in ART may lead not only to abrupt drops in CD4+ T cell counts and development of opportunistic infections, but also cardiovascular events, as proven in the SMART trial where all-cause mortality rates almost doubled and opportunistic infection related death rates almost tripled in the group that was assigned to the episodic antiretroviral therapy guided by CD4+ T cell counts (treatment was interrupted and reinstated only when CD4+ counts dropped to 250 cells/μL or if patients developed opportunistic infections). Frequent interruptions and poor adherence may also lead to development of antiviral resistance, which once acquired is perpetuated lifelong and may lead to a need for more complex regimens.

Close monitoring of viral load and basic labs is important especially in the first year of treatment, when visits and laboratory testing is more frequent. Virologic failure is the inability to achieve or maintain suppression of viral replication to HIV RNA level <200 copies/mL and should be promptly addressed with genotypic testing that can determine drugs to which the virus may have become resistant and can guide informed changes in ART that can lead to virologic suppression. This should be coupled with additional counselling regarding adherence. Lack of adherence may be related to mental health disorders and neurocognitive impairment, substance use, cost, unstable housing, adverse drug effects, and pill burden.

Huge advances in drug development led to easier to tolerate regimens with less side effects, smaller pill burden and minimal interactions. Daily drug regimens are preferred.

Integrase strand transfer inhibitors (INSTI) have become the mainstay of treatment in the past decade, as protease inhibitors (PI) have more side effects, interactions and toxicities and non-nucleoside reverse transcriptase inhibitors (NNRTI) have a lower barrier to developing resistance and undesirable side effects. Due to its efficacy

and relatively high barrier to resistance, tenofovir has been one of the most used nucleotide reverse transcriptase inhibitor (NRTI) not only for treatment, but now also for preexposure prophylaxis. A newer formulation (tenofovir alafenamide) led to a smaller pill size but more importantly reduced effects on renal function and bone density loss that made the older formulation (tenofovir disoproxil) less desirable.

Newer injectable options were approved in 2021, including a long-acting combination of an INSTI (cabotegravir) and an NNRTI (rilpivirine) that can be administered monthly in a clinical setting as intramuscular injection. Newer classes of drugs that inhibit viral entry into human cells, including a CCR5 coreceptor inhibitor, a fusion inhibitor, an attachment inhibitor, and a post-attachment inhibitor monoclonal antibody offer options to individuals with multi-class resistance.

Question 4

During the first 2 years after her diagnosis, patient presented regularly to clinic appointments, viral load became undetectable on ART, but subsequently she was lost for follow up and after a gap in care of 5 years she presents to clinic complaining of weight loss and malaise and now has a CD4 of 40 cells/μL. Along with restarting ART, which of the following opportunistic infections should be considered for antimicrobial/antifungal primary prophylaxis?

A. Cryptococcal meningitis
B. Disseminated *Mycobacterium avium* complex (MAC)
C. Pneumococcal pneumonia
D. *Toxoplasma gondii* meningoencephalitis
E. Disseminated histoplasmosis

Answer and Explanation

Answer: D

Only *Pneumocystis jirovecii* and *Toxoplasma gondii* require primary prophylaxis in patients with AIDS and a CD4 count <200 cells/μL. Toxoplasma reactivation occurs more frequently at CD4+ counts under 150. Cryptococcus and MAC infections usually appear when T cell counts drop below 50, however primary prophylaxis is not indicated due to toxicity, lack of efficacy, and concerns of resistance developing with monotherapy. The lower the CD4+ counts, the higher incidence of Pneumococcal pneumonia, however prophylaxis is done with vaccination rather than antimicrobials. Prophylaxis for disseminated *Histoplasma capsulatum* infections is considered only in hyperendemic areas outside US. Primary prophylaxis presumes that the patient does not currently have a particular opportunistic infection. If this patient had symptoms consistent with any of the above infections, a directed workup would be indicated rather than simply starting primary prophylaxis.

4 Opportunistic Infections

While at the beginning of the HIV epidemic, a diagnosis of HIV was an almost certain death sentence, the current life expectancy of an infected person under ART is similar to the average lifespan of general population. Following initiation of an effective combination antiretroviral treatment (ART), a rapid decline in the viral load is expected, with a goal to achieve a viral load of less than 50 copies/μL within 6 months and somewhat slower rise in CD4+ count. Not infrequently, when ART is initiated at CD4+ counts of less than 50 cells/μL, the immune reconstitution is only partial and some patients remain lifelong at low CD4+ counts, albeit the risk for opportunistic infections remains low if the HIV viral load remains undetectable.

When considering opportunistic prophylaxis, one should take into consideration prior infections, exposures, serologies, and geography. Will discuss only a few of the most common opportunistic infections.

Pneumocystis jirovecii is a ubiquitous fungus that caused infections in 80% of AIDS patients before effective ART era and is a significant cause of mortality in untreated individuals with a CD4 countless than 200 cells/μL. Typically patients present with a dry cough, fever and dyspnea exacerbated by minimal effort. The chest radiography typically shows bilateral perihilar infiltrates, and computer tomography may show bilateral ground glass opacities and occasionally pneumatoceles or cysts that can rupture and result in pneumothorax. See more details on diagnosis below in Case 2. The preferred agent both for primary prophylaxis and treatment is trimethoprim/sulfamethoxazole (TMP-SMX), alternate prophylaxis regimens include dapsone and atovaquone. In the case of dapsone, G6PD deficiency should be ruled out to prevent hemolysis. Monthly inhaled pentamidine is used for individuals who cannot tolerate other options. Treatment options for sulfa allergic patients include clindamycin with pyrimethamine or as a last resort intravenous pentamidine, which has higher toxicity.

Toxoplasma gondii is a protozoan parasite that becomes symptomatic in immunocompromised patients through reactivation of a latent infection, however primary disseminated infections can occur. Risk factors include accidental ingestion of oocysts shed in cat feces and sporulated in the environment, eating undercooked meat or raw shellfish. Most common manifestation is encephalitis which usually presents with headaches, fever, and confusion; focal neurological abnormalities depend on location of lesions. Seizures, vision loss, and coma can develop. CT and MRI brain imaging show usually multiple ring-enhancing lesions and differential diagnosis includes lymphoma, tuberculosis, brain abscess. Treatment is usually started empirically, and brain biopsy (definitively diagnostic but carrying significant morbidity) is pursued only if response is not seen after 2 weeks

of treatment. CSF toxoplasma PCR can be used for diagnosis if a lumbar puncture is not contraindicated. A negative serum IgG suggests alternative diagnosis, and a positive CSF EBV PCR suggests primary CNS lymphoma. CSF serology and serum IgM are not useful in making a diagnosis. IgG seropositive patients with a T cell count <100 cells/μL should receive prophylaxis and continue until CD4 count increases to >200 cells/μL for 3 months. The combination of choice for treatment is pyrimethamine plus sulfadiazine plus leucovorin, but high dose TMP-SMX is also effective and better tolerated. TMP-SMX is also used for prophylaxis. Pyrimethamine and leucovorin are added to dapsone in individuals with sulfa allergies (Table 2).

Mycobacterium avium complex (MAC) can cause a disseminated infection in individuals with a CD4 <50cells/μL. Organisms are ubiquitous in the environment. Patients present with fever, weight loss, fatigue, diarrhea, and abdominal pain. Laboratory abnormalities include anemia and elevated alkaline phosphatase. The organisms can be isolated from blood and bone marrow cultures. Historically, prophylaxis with a weekly macrolide was offered, however, due to lack of efficacy and concerns with development of resistance to macrolide monotherapy, the newest DHHS guideline recommends limiting prophylaxis only to individuals who cannot receive ART or do not have fully suppressive regimens available and remain viremic. Treatment consists of two or more agents, one of which should be a macrolide (clarithromycin or azithromycin). Subclinical infections may become evident in patients who initiate ART at low CD4 counts of <50 cells/μL, when patients may develop an immune reconstitution inflammatory syndrome (IRIS) manifesting as fever and painful lymphadenopathy within weeks of starting ART.

Table 2 Opportunistic infection prophylaxis

T cell counts (cells/μL)	Opportunistic infection	Primary prophylaxis (no preexistent disease)
All CD4 counts	Tuberculosis (TB)	Screen with IFNγ assay or PPD and treat latent TB
	HSV	Chronic suppression with acyclovir or valacyclovir for frequent recurrences only
<250	Coccidioidomycosis	Preemptive therapy in endemic area (Arizona, California) with fluconazole if seropositive
<200	Pneumocystis	Daily TMP-SMX double strength or single strength *or* Dapsone *or* Atovaquone *or* Aerosolized Pentamidine
<150	Histoplasmosis	Not recommended in US (lack of proven efficacy) Itraconazole is used in hyperendemic areas in South America
<100	Toxoplasma	Daily TMP-SMX double strength or single strength Dapsone + pyrimethamine + leucovorin
	Cryptococcus	Not recommended (lack of efficacy and potential development of resistance)
<50	MAC	Not recommended (monotherapy with macrolides has poor efficacy and potential development of resistance)
	CMV	Not recommended even if viremia is present (no benefit in the absence of end organ symptoms)

Cryptococcus neoformans is the main causative species of cryptococcosis in US. Exposure to dried aerosolized bird droppings may increase the risk of acquisition, but the organism is ubiquitous in environment. In people with HIV with a CD4 <50–100 cells/μL meningoencephalitis is the most common presentation, with malaise, headache, and fever developing subacutely, and meningismus being much less common than in bacterial meningitis. Altered mentation, lethargy and personality changes can also be seen. Disseminated infection, isolated lung infections, and skin involvement can be seen. Skin lesions are nodular, umbilicated, usually larger than molluscum and can ulcerate. Frequently, the serum cryptococcal antigen is positive but CSF analysis is diagnostic, with lymphocytic pleocytosis, elevated protein levels and detection of cryptococcus antigen. Opening pressure can be severely elevated and may require repeated lumbar punctures or even placement of shunts, as antifungal treatment leads to very slow improvement. Induction with amphotericin deoxycholate or with lipid formulations with the addition of oral flucytosine is usually continued for 2 weeks or until the CSF fungal cultures become negative. Cryptococcal antigen titer should not be used to guide treatment, but a high titer can be a poor prognostic factor, along with a low number of lymphocytes in CSF. Prolonged consolidation and secondary prophylaxis with oral fluconazole are usually required and cryptococcal antigen can persist for extended periods. Cryptococcal IRIS after initiation of ART in patients with unrecognized disease can be very severe and can lead to negative outcomes including death related to severe increase in intracranial pressure. ART initiation should be delayed at least 4–6 weeks after starting treatment for CNS cryptococcosis, to avoid such outcomes.

Question 5

Along with her, she brings her current male partner who tested negative recently for HIV. The couple is asking for advice on preventing transmission. You advise them that:

A. Male circumcision reduces the transmission to negligible levels
B. Using condoms was proven to be the most reliable method of preventing transmission

C. Preexposure prophylaxis for the HIV negative male partner would be highly effective
D. They should use vaginal preparations of antiretrovirals
E. The HIV negative partner should receive the HIV vaccine

Answer and Explanation

Answer: C

Unfortunately, to date, all attempts at developing an HIV vaccine have led to failure. Currently, the best strategy to reduce transmission is treatment of HIV positive individuals. When achieving undetectable HIV viral loads as a result of consistent and effective ART, sexual transmission is reduced to negligible rates, which led to the concept of "undetectable = untransmissible" (U=U) through treatment as prevention. Vaginal preparations of tenofovir have lower efficacy than systemic PrEP and while dapivirine vaginal ring is now an option for HIV negative women at risk for HIV acquisition outside of USA, it is not FDA approved and would not be indicated in this couple's situation. Systemic preexposure prophylaxis with a combination of 2 oral or injectable antiretrovirals are viable options especially if the couple is not monogamous, and the HIV positive individual does not have reliably undetectable HIV viral loads. Condoms are theoretically highly effective at prevention, have the advantage of reducing transmission of other STIs along with HIV, and they may be acceptable to many couples, but due to inconsistent use and cost, the real-life efficacy is not as high as with systemic ART. Circumcision does reduce transmission, but it is not reliable enough to be recommended as the sole method of prevention.

5 HIV Prevention

The risk of HIV acquisition by sex is highest with receptive anal intercourse (1 in 72 sex acts), followed by insertive anal intercourse (1 in 900 sex acts), receptive penile-vaginal intercourse, insertive penile-vaginal intercourse, with oral sex being the lowest but of note not completely zero risk. Concomitant STIs, especially ulcerative genital diseases (mainly HSV and syphilis) greatly increase the risk of transmission.

Male circumcision was proven to reduce female to male transmission in half in an African study, however the male to female transmission (transmission is likely related to genital secretions) is not affected and male to male transmission was not studied.

Preexposure prophylaxis (PrEP) with co-formulated tenofovir disoproxil and emtricitabine taken daily by individuals at risk for acquiring HIV can all but eliminate transmission as long as adherence is appropriate. The combination is well tolerated, but it requires frequent monitoring, and it is not devoid of side effects that may include bone density loss and kidney disease with prolonged use. Tenofovir alafenamide, a newer formulation, reduces these side effects, but is less effective in cisgender women at risk for acquiring HIV. Acquired drug resistance and transmission of virus that is resistant to the combination are rare. Long-acting injectable cabotegravir was FDA approved in December of 2021; it was shown to reduce transmission in a cohort of men who have sex with men and transgender women, when compared to tenofovir/emtricitabine. This field is rapidly evolving and additional studies are likely to provide more information in regards to other populations at risk.

For injection drug users, needle exchange programs and opioid addiction treatments have been associated with reduced transmission. On the other hand, the increase in opioid addiction rates in rural America, lack of screening, education and limited support for addiction treatment has led to an increase in HIV in these areas and even outbreaks as the one in southern Indiana in 2015.

Mother to child transmission via intrauterine and intrapartum route in the absence of treatment occurs in 24% of infected mothers but drops below 0.2% in women who start ART prior to pregnancy and maintain an undetectable viral load. The risk for transmission is incrementally higher in women who initiate ARVs during pregnancy, the later the initiation the higher the risk, reaching 2.2% in women who initiate ARVs in the last trimester. Scheduled cesarean sections are indicated only for mothers who do not achieve viral loads of <1000 copies/mL near time of delivery. In addition, intravenous zidovudine is administered intrapartum, and infants are started on presumptive HIV therapy at birth. On the other hand, for women who achieve an undetectable viral load of <50 copies/mL, the mode of delivery is determined by obstetric indications and intrapartum zidovudine is not required.

Case 2

A 33-year-old cisgender man, with history of HIV diagnosed 10 years prior to the presentation was seen in the outpatient clinic for dyspnea with minimal exertion for at least a month. He was lost for follow up, had a history of nonadherence to medications and at the time of presentation was not taking either the previously prescribed regimen of antiretrovirals nor any antibiotics for prophylaxis. He was never previously admitted to a hospital and had no known comorbidities and did not travel out of state in the past 10 years. Dyspnea was associated with a dry nonproductive cough. Patient denied hemoptysis. He endorsed 10 lb weight loss and intermittent low-grade fever. CD4+ lymphocyte count was 22 cells/μL. Creatinine was within normal limits. Upon examination, patient had extensive whitish deposits on tongue and palate consistent with oropharyngeal candidiasis, however his lungs were clear to auscultation with no crackles or rhonchi and there was no dullness on percussion. Heart exam was normal, he did not have any visible rash and there was no leg edema. He was hypoxic, with an oxygen saturation of 89%

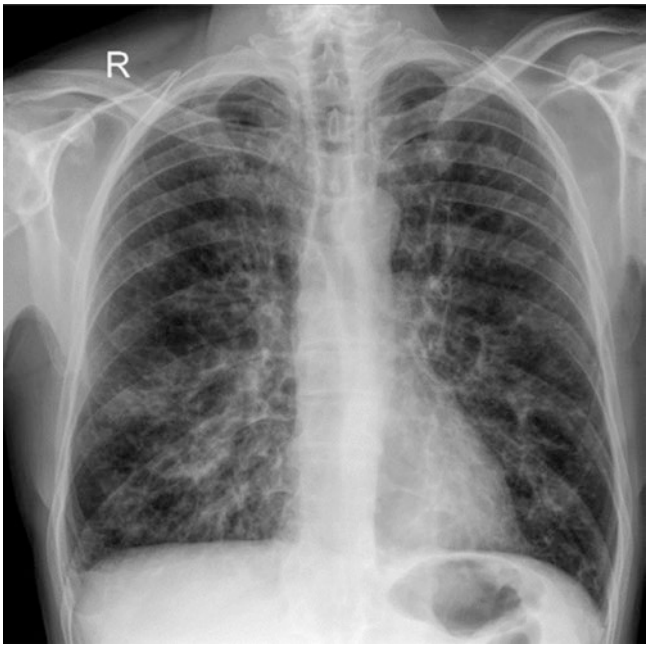

Fig. 3 Anteroposterior chest X-ray showing bilateral lung opacities. (With permission from Ramos AL et al. *International Journal of Infectious Diseases*, 2022-02-01, Vol. 115, pp. 185–188 [3])

on room air at rest and 75% after minimal effort. A chest radiograph showed bilateral infiltrates as seen in Fig. 3.

Question 1

What is the most likely etiology of the pulmonary infiltrates?

A. *Coccidioides immitis*
B. *Streptococcus pneumoniae*
C. Influenza A virus
D. Heart failure with reduced ejection fraction
E. *Pneumocystis jirovecii*

Answer and Explanation

Answer: E

Based on his history of uncontrolled HIV with a very low CD4+ count, this patient is at risk for a plethora of opportunistic infections (see Table 3), however common pathogens like influenza and noninfectious causes must be kept in the differential diagnosis. The most likely pathogen that causes dyspnea, a dry cough and bilateral infiltrates would be *Pneumocystis jirovecii*. Patients with a CD4+ of less than 200 and unsuppressed viremia are at significant risk for acquiring Pneumocystis pneumonia. The presentation is insidious, main symptoms include dyspnea, fever, sometimes cough, with no sputum production. While chest radiography can reveal infiltrates, many times bilateral, atypical presentations are frequent, from unilateral infiltrates to cavitary lesions. A significant number of cases have very vague findings on imaging, and only computer tomography may reveal the infiltrates. Pneumonia is a common presentation for patients who are newly diagnosed with HIV/AIDS, and *Streptococcus pneu-*

Table 3 Most common pulmonary complications in HIV infected individuals

Complication	Comments/"buzz words"
Infections	
Streptococcus pneumoniae	Most common bacterial infection; vaccine preventable
Haemophilus species	
Staphylococcus aureus	More common in PWID
Pseudomonas aeruginosa	Hospitalized patients with tracheostomy, ventilator exposure, Gram negative non-lactose fermenter in sputum culture
Mycobacterium tuberculosis	At any CD4+ count; person to person transmission; MDR/XDR cases more common in HIV
Mycobacterium avium complex	Rarely pulmonary, more often disseminated in AIDS
Nocardia spp.	Concomitant brain lesions, branching weakly AFB positive organism, prolonged combination drug therapy
Rhodococcus	Horse exposure; short gram positive rods
Pneumocystis jirovecii	Most common opportunistic infection at <200 T cells
Cryptococcus neoformans	More common meningoencephalitis than pneumonia; umbilicated skin lesions; serum antigen usually positive; high risk of IRIS
Histoplasma capsulatum	Ohio and Mississippi river valleys; urine antigen
Coccidioides immitis	Dry arid southwest US states; interstitial/cavitary pattern
Aspergillus species	Rare in HIV infection
Blastomyces dermatitidis	Central US; large skin lesions; broad based budding
Talaromyces (Penicillium) marneffei	Southeast Asia
Cytomegalovirus	More commonly involves colon than lung in AIDS
Toxoplasma gondii	Cat feces, raw meat; more frequent brain lesions
Malignancies	
Kaposi sarcoma	15% have isolated lung lesions, skin lesions are typical violaceous; high risk in MSM; HHV8 infection
Non-Hodgkin lymphoma	B-cell origin; EBV associated
Non-small cell lung cancer	More common than in HIV negative population possibly due to higher incidence of smoking; older than 50
Interstitial pneumonitis	Clinically indistinguishable from PCP, but CD4 >200
Other	
COPD	Likely due to higher incidence of smoking
Sarcoidosis	Usually at CD4 >200
IRIS	Infections, sarcoidosis, tumors, autoimmune conditions

moniae is likely the most common pathogen, however the presentation is much more acute, fever is more common, the lung exam is usually abnormal and reveals consolidation and rhonchi. The diagnosis suspicion is higher if the infiltrates are lobar and confirmation can be made with sputum Gram stain and culture, as well as the streptococcus urine antigen.

Question 2

Which of the following diagnostic methods can be used for Pneumocystis pneumonia?

A. Gram stain form expectorated sputum
B. PAS (Periodic acid–Schiff) stain from a transthoracic needle biopsy
C. Pneumocystis PCR from serum
D. Galactomannan antigen from serum
E. GMS (Gomori methenamine silver) stain from bronchoalveolar lavage (BAL) fluid

Answer and Explanation

Answer: E

Expectorated and induced sputum specimens have a low sensitivity for diagnosis of *Pneumocystis jirovecii* pneumonia (PCP). In addition, obtaining sputum can be very challenging, as the cough, if present, is usually nonproductive. Confirmation of diagnosis is recommended, since no clinical or radiological features are specific enough. In addition, treatment is prolonged and potentially toxic. Missing an alternative diagnosis may lead to significant morbidity and mortality. In addition, some immunocompromised patients including patients with AIDS can present with multiple opportunistic infections. While molecular methods of diagnostic are becoming broadly available and pneumocystis PCR from sputum has very high sensitivity and specificity, it may not be available in all clinical settings. Silver stain and immunofluorescence from BAL or from lung biopsy remain the gold standard. Transthoracic needle biopsy is rarely employed due to the increased risk of pneumothorax and other complication, as well as availability of less invasive methods. Nonspecific, but supportive of diagnosis are elevated 1–3-beta-D-glucan, elevated LDH. PCP can occasionally be encountered in patients with a CD4+ cell count of over 200 cells/μL especially in the absence of HIV viral load suppression. On the other hand, even in the absence of a very robust immune reconstitution, PCP is uncommon in individuals with a fully suppressed HIV viral load (undetectable).

Question 3

The patient was hospitalized due to hypoxia, was administered supplemental oxygen; TMP-SMX as well as prednisone was initiated, with a presumptive diagnosis of pneumocystis pneumonia. In addition, thrush had to be addressed. Antiretrovirals were not restarted at this point. Review of chart showed that he received multiple antiretroviral regimens since his diagnosis. He had not developed any side effects, but adherence was poor, and he never achieved complete viral suppression. He was lost for follow up for 4 years and did not take any medications during this time. Current HIV viral load is 5.2 million copies/mL. Select the correct statement regarding thrush (oropharyngeal candidiasis) in patients with HIV:

A. The diagnosis of thrush should always be confirmed with a fungal culture from a mucosal scraping
B. Oropharyngeal candidiasis is diagnosed by mucosal biopsy
C. Treatment of choice for thrush in pregnant women is fluconazole
D. Majority of patients with HIV carry fluconazole resistant strains of candida
E. The diagnosis of oropharyngeal candidiasis is clinical

Answer and Explanation

Answer: E

Oropharyngeal candidiasis occurs frequently in patients with CD4 counts less than 200 cells/μL and it may be the first manifestation in patients newly diagnosed with HIV, however thrush can be encountered in individuals with higher counts, especially if comorbid conditions including uncontrolled diabetes and incorrect use of inhaled steroids exist. The most common presentation of candidiasis is the pseudomembranous candidiasis or thrush; however, angular cheilitis and erythematous (also known as atrophic) candidiasis can be encountered. The presumptive diagnosis is clinical and only rarely confirmation with a potassium hydroxide wet mount, Gram stain or a culture are required. One should differentiate between candidiasis and other conditions encountered in patients with HIV:

- Oral hairy leukoplakia—presents as raised white lesions distributed mainly on the lateral aspect of the tongue), which do not require any specific treatment and usually resolve along with immune reconstitution in patients on antiretrovirals; these lesions are highly adherent to the tongue and cannot be removed with a tongue depressor.
- Ulcerations caused by herpes simplex and aphthous stomatitis can look similar, but usually herpetic lesions involve the vermillion border and aphthous ulcers are found on the buccal mucosa; HSV DNA PCR testing can differentiate these two conditions when in doubt (cultures are less sensitive and more time consuming). Herpes simplex responds to acyclovir derivatives and resistance is uncommon, but prolonged intermittent use can lead to selection of resistant virus. Aphthous stomatitis can be more frustrating, as the response is variable to topical steroids, anti-inflammatory mouth washes, tetracyclines and even thalidomide for severe cases. Cytomegalovirus occasionally can produce mucosal lesions, but the most common location for mucosal ulcerations would be the esophagus and lower gastrointestinal tract.

- Oral warts secondary to human papillomavirus infection—raised nonpainful lesions—diagnosis can be confirmed by biopsy which is usually indicated if suspicion for a malignant lesion exists.

Fluconazole is the drug of choice in the treatment of oropharyngeal candidiasis. Due to potential teratogenicity of fluconazole especially in the first trimester, the preferred treatment in pregnancy is topical, with miconazole, clotrimazole, or nystatin. Fluconazole resistant candidiasis is still rare, treatment is challenging and may include intravenous echinocandins. Some fluconazole resistant strains retain susceptibility to newer azoles, including posaconazole and voriconazole.

Question 4

Three days after starting fluconazole thrush has resolved. Seven days into the treatment with TMP-SMX and prednisone, the patient continues to be dyspneic, oxygen requirements fail to improve and intermittently he has low-grade fever. Alternative diagnoses are being entertained. The diagnosis of pulmonary histoplasmosis should be higher in the differential if:

A. He lives in southern Ohio and raises pigeons
B. He was recently released from being incarcerated for 5 years
C. He travelled to southeast Asia
D. He is of Asian descent and lived for the past 10 years in Arizona
E. He recently noticed several dark violaceous lesions on his chest

Answer and Explanation

Answer: A

Exposure to bat guano or bird droppings and location endemic for histoplasmosis suggests this diagnosis. Incarceration increases the risk of tuberculosis. Travel to south-Asia increases the risk of acquisition of a dimorphic fungus—*Talaromyces marneffei*. Dark violaceous lesions suggest Kaposi sarcoma.

6 Differential Diagnosis of Lung Lesions in a Patient with HIV

While Pneumocystis pneumonia is still the most common AIDS-defining opportunistic infection in US, alternative diagnoses should be considered when faced with a patient with HIV and pulmonary infiltrates.

Persons with HIV are at increased risk for developing tuberculosis and exposure to environments with higher incidence: living in densely populated areas with higher incidence of tuberculosis, visiting or migrating from endemic countries (in Africa, TB is the most common pulmonary complication in HIV).

Endemic mycoses should always be considered, depending on travel and state of residence: histoplasmosis is endemic in the Ohio and Mississippi River valleys, but also in many areas of Central and South America. Travel or residence in dry areas in Southwestern US should raise suspicion for coccidioidomycosis. *Talaromyces marneffei* can cause pulmonary and disseminated infections in HIV infected individuals from Southeast Asia. The only one endemic mycosis that requires primary prophylaxis in US is coccidioidomycosis in patients with positive serology, no symptoms and a CD4 <200 cells/μL.

Toxoplasma gondii, while well known to cause brain lesions in individuals with a CD4 count below 100cells/μL, can also cause pulmonary infections. Negative serology makes this diagnosis unlikely, however a positive IgG is not sufficient for confirmation and represents either evidence of prior exposure or active disease, the diagnosis being made by direct observation of tachyzoites in a bronchoalveolar lavage. Prophylaxis with TMP-SMX reduces the rate of reactivation of a latent infection. Alternatives for individuals with sulfa intolerance include dapsone or atovaquone plus pyrimethamine and leucovorin.

The differential of lung lesions with HIV can be extensive and more than one condition can be found in the same individual. Some opportunistic infections found in other immunocompromised hosts (i.e., transplant recipients and cancer patients), including aspergillosis, CMV infection, and nocardiosis are not as common in persons living with HIV. Noninfectious causes of lung lesions should also be considered, as interstitial lung disease and sarcoidosis are more prevalent than in HIV negative population; however, these conditions usually are found in HIV patients with higher CD4 counts (>200 cells/μL).

Question 5

Despite starting prednisone and TMP-SMX at appropriate doses as empiric treatment for PCP pneumonia, the patient fails to improve after the first week of treatment. He continues to be hypoxic and has intermittent fevers. A decision is made to pursue a bronchoscopy, which reveals no purulence, however several violaceous patches are seen throughout the bronchial tree. The bronchoalveolar lavage specimen is negative for fungal, acid-fast smears and Gram stain does not reveal any microorganisms. PCR for pneumocystis is negative (Fig. 4).

The most likely diagnosis at this point is:

A. Bronchogenic carcinoma
B. Pulmonary Kaposi sarcoma
C. Bacillary angiomatosis
D. Non-Hodgkin lymphoma
E. Histoplasmosis

Answer and Explanation

Answer: B

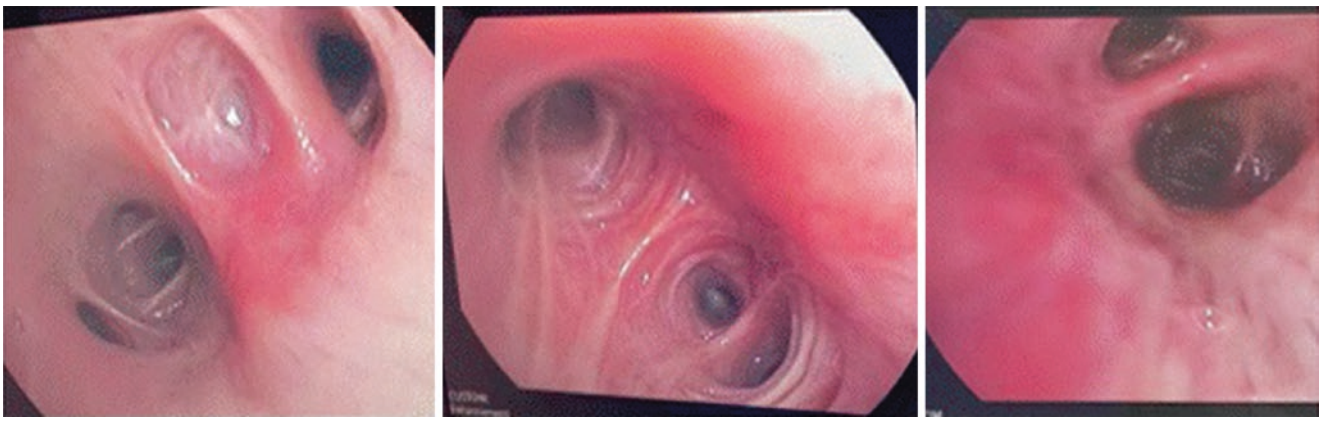

Fig. 4 Purple and erythematous lesions observed during bronchoscopy. (With permission from Ramos AL et al. Pulmonary Kaposi's sarcoma—an atypical clinical presentation. *International Journal of Infectious Diseases*, 2022-02-01, Vol. 115, pp. 185–188 [3])

The bronchial lesions seen on bronchoscopy are diagnostic for Kaposi Sarcoma (KS), a malignancy related to HHV8 infection. Usually, a biopsy is not required for diagnosis, both the skin lesions and the appearance of bronchial lesions are very typical. Pulmonary involvement can be associated with pleural effusions. While majority of patients with pulmonary KS have skin lesions, about 15% have only visceral involvement. Immune reconstitution is essential for treatment, however for extensive skin involvement as well as for visceral involvement, there is a need for addition of systemic chemotherapy. A significant number of patients with KS do have an opportunistic infection, making a comprehensive workup necessary, without early closure.

Final diagnosis: Pulmonary Kaposi Sarcoma in a patient with HIV/AIDS.

7 Conclusions

HIV continues to be mainly transmitted via sexual contact. Key changes in diagnosis and management in the past two decades include new diagnostic tools that reduce the window period to as little as 2 weeks by using the p24 antigen and treatment offered as early as immediately after diagnosis, in order to preserve the immune system, especially the gut residing lymphocytes from viral aggression and prevent transmission. New antiretrovirals are better tolerated and have lower pill burden. Options for resistant virus are being developed. PrEP, screening and treating pregnant women, as well as strategies to educate and treat intravenous opioid addiction are additional tools for preventing transmission. Opportunistic infections have decreased significantly in frequency along with the scale-up of effective ART but remain prevalent in untreated populations. Malignancies can mimic some opportunistic infections and careful evaluation may uncover multiple simultaneous opportunistic conditions.

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