HIV RELATED OPPORTUNISTIC INFECTIONS: A SYSTEM WISE APPROACH
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ABSTRACT: HIV infection predisposes to various opportunistic infections. The profile of opportunistic infections in India is different from Western studies. Mycobacterium tuberculosis is the most common opportunistic infection in India while atypical mycobacterial infections and kaposi sarcoma are relatively rare here as compared to western populations. In general oropharyngeal candidiasis, Mycobacterium Tuberculosis and cryptosporidial diarrhea form the most common opportunistic infections in HIV patients in India. The opportunistic infections are under diagnosed in Indian scenario. Adequate primary and secondary prophylaxis of opportunistic infection, and treatment is necessary to improve mortality caused by them in HIV patients.

KEYWORDS: HIV, opportunistic infection, pneumocystis, candida, tuberculosis.

INTRODUCTION: HIV increases predisposition to commonly occurring infections like tuberculosis and pneumonia. It also increases likelihood of certain AIDS defining opportunistic infections (OI) which are specific to HIV like pneumocystis jirovecii, cryptosporidium and cryptococcal meningitis. The profile of the opportunistic infections changes with stage of HIV and viral load (Figure 1).

Mycobacterium tuberculosis is the most common opportunistic infection in India while atypical mycobacterial infections and kaposi sarcoma are relatively rare here as compared to western populations. In general oropharyngeal candidiasis, Mycobacterium Tuberculosis and cryptosporidial diarrhea form the most common opportunistic infections in HIV patients in India.¹

It is important to remember that profile of opportunistic infections in India is different from western studies. The profile of opportunistic infections in Tuberculosis is summarized in Table 1 based on data from big Indian cohort studies of HIV patients done in last decade. This article will focus on HIV related respiratory, gastro-intestinal, cardiac and CNS manifestations with a focus on infections.

HIV related respiratory Infections: Respiratory system is commonly involved in HIV. Patients having respiratory infection present with non-specific symptoms like cough, chest pain, difficulty breathing with other manifestations suggestive of HIV like weight loss, chronic Diarrhea, oral thrush and unusual infections. Thus, it becomes imperative to diagnose the causative respiratory pathogen from non-specific constellation of symptoms in an immunosuppressed patient and treat it accordingly. Following are few of the most common respiratory infections afflicting HIV patients in Indian scenario.

Tuberculosis: Mycobacterium Tuberculosis is one of the most common OI s in Indian scenario. In many Indian case series it was second only to oral candidiasis. Almost 35-50% of patients presenting to a primary care provider have been reported to have HIV²,³,⁴
M. Tuberculosis infection may occur at any point in course of HIV disease unlike otter OIs with non-specific symptoms like fever and cough. In patients with lower CD4 counts, these symptoms will be less marked.

We traditionally have relied upon chest x-ray and sputum for AFB to diagnose pulmonary Tb. However in HIV patients the sensitivity and specificity of these traditional tools suffer. Classical finding of upper zone cavitation and opacity are less common in HIV patients, more so in patients with lower CD4 counts. Chest x-ray may be even normal in 10-20% cases. Sputum for AFB is less sensitive for diagnosing pulmonary tuberculosis in HIV patients as compared to non-HIV adults with sensitivities ranging from 20-40% in various studies.²

Due to this, WHO now recommends a new generation nucleic acid amplification test called CBNAAT as a first line test for diagnosing TB from sputum samples in HIV patients instead of microscopy. Further, CBNAAT is helpful in finding drug resistant TB cases and ruling out atypical mycobacterium infections within a span of 2 hours. Other measures like lymph node biopsy, pleural fluid analysis, BACTEC culture can be of help in establishing the diagnosis of TB in patients with atypical presentations.

After making the diagnosis standard treatment with intensive phase (HRZE for 2 months) and (HR for 4 months) is advised in most cases.⁵⁻⁷ The current WHO recommendation is to start ATT in patients as soon as it is detected regardless of risk of IRIS (immune reconstitution inflammatory syndrome). Efavirenz based HIV regime is used in patients taking ATT. Patients should be advised about adherence to Anti tuberculous chemotherapy to prevent development of resistance.

**Pneumocystis jirovecii Pneumonia**: Pneumocystis is a common OI affecting lung of HIV patients, particularly when CD4 falls below 200 cells/µl. Its prevalence has been decreasing in western world in age of HAART and Pneumocystis prophylaxis. Various studies in India have reported that Pneumocystis has prevalence of 15-25 % in HIV patients presenting to a primary care provider. Pneumocystis generally presents with insidious symptoms like progressive exertional dyspnea and cough characteristically over a period of month in contrast to tuberculosis and bacterial pneumonia which typically are associated with fever. These symptoms with other AIDS defining features should immediately alert the treating physician to possibility of Pneumocystis.⁸

Physical signs are frequently absent in Pneumocystis. Chest X ray shows diffuse interstitial infiltrates in severe form while it may be normal or with infiltrates in mild form. Patient generally has fall in oxygen saturation upon 6 minute or 10 minute walking test. Currently, diagnosis of Pneumocystis pneumonia relies on direct visualization of Pneumocystis cysts or trophic forms from stained respiratory specimens.⁹¹⁰

Though diagnosis of Pneumocystis is suspected clinically and radiologically suspected, it should be confirmed generally by using immunofluorescent or more conventional (Giemsa or methenamine) stains. Now a day’s more sensitive and specific PCR techniques are available for diagnosing Pneumocystis. The respiratory specimens are obtained generally by induced sputum, however if induced sputum is negative or patient is unable to produce sputum Bronchoalveolar lavage should be used.

Oxygen saturation should be measured prior to initiating Pneumocystis therapy both at rest and while ambulating; arterial blood gas measurement should be obtained to assess the need for adjunctive corticosteroids. Cotrimoxazole (two double-strength tablets eight hourly) is the preferred
oral regimen for PCP. Patients who experience treatment failure (no improvement after 5 days of therapy) awhile on an oral regimen should be switched to an intravenous regimen.

All Patients with PCP should be treated with a 21-day course of anti-Pneumocystis therapy.\textsuperscript{11,12} (S. Patients with an ABG showing a P02 < 70 mmHg or less, or A-a O2 gradient > 35 mmHg or more should also receive steroids or hospitalized. Patients who are unable to eat or are very sick should be given IV Cotrimoxazole or IV clindamycin –oral primaquine therapy. Initiating therapy with ART should generally be delayed until after the acute respiratory co. Patients with PCP who are on ART should be continued on it. Empiric therapy of Pneumocystis is discouraged as steroids used in therapy of severe PCP may be harmful in other differentials of Pneumocystis like M. Tb.

**Bacterial Pneumonia:** Bacterial pneumonia is caused by regular pathogens like streptococcus pneumonia even in HIV patients. However frequency and severity of infection increases with falling CD 4 counts. HIV should be suspected when bacterial pneumonia occurs with increasing frequency in a patient with no other co morbidities. IDSA recommends administering the 23-valent pneumococcal polysaccharide vaccine to HIV positive adults and children with CD4 >200 as soon as HIV infection is diagnosed (providing that they have not had the vaccine during the previous five years). The duration of the protective effect of primary immunization is unclear. Single revaccination after five years is recommended which is similar to recommendations in non-HIV patients.

**Bacterial Sinusitis:** Bacterial sinusitis occurs with higher frequency and severity in HIV individuals. Patient typically presents with fever headache nasal tenderness. Atypical organisms like pseudomonas are common causes of bacterial sinusitis in HIV patients. Aspergillus can also cause sinusitis in patients with CD4<150. Patients must be treated adequately or sinusitis can easily become chronic.

**Penicilliosis:** This fungal infection is more common in north east part of India. Most patients present with fever weight loss, lymphadenopathy, and skin lesions.\textsuperscript{13,14} However one third patients have pulmonary symptoms as well and they present with chest x ray showing diffuse reticulo-nodular shadows.\textsuperscript{15,16} Diagnosis is established by fungal culture or histopathology of specimens and treatment. Patients are treated with oral itraconazole or IV Amphotericin depending upon severity of infection.\textsuperscript{17}

**Gastrointestinal Infections:**

**Cryptosporidium, Microsporidium spp and Isospora:** Cryptosporidiosis is among the AIDS defining illness as per CDC guidelines. It is one of the most common parasitic infections of the GI tract in AIDS patients. Among Southeast Asian countries the infective rate is almost 40\%. Cryptosporidiosis commonly occurs when the CD4 count is less than 200cells/µl in a patient with HIV infection.\textsuperscript{18} Clinical presentation of cryptosporidiosis is chronic diarrhea with watery stools, Dehydration, Abdominal pain, Weight loss. The diarrhea is non-inflammatory and oocyte with acid fast stain is characteristic finding.\textsuperscript{19,20} Microsporidium spp. and Isospora belli infections are also prevalent among the AIDS patient.
The presentation and clinical picture is similar to cryptosporidiosis. Therapy is predominantly supportive and effective ARV therapy leads to marked improvement. Nitazoxanide therapy in doses up to 2000mg/d is associated with improvement in symptoms of cryptosporidium related diarrhea. Albendazole in dose of 400mg BID can be used for Microsporidium. Isospora is treated with TMP /SMX and thrice weekly regimen can be used to prevent recurrence.

**ENTAMOeba Histolytica:** It is among the most common parasitic disease in both developing and developed countries. E. Histolytica has the ability to disrupt the intestinal mucosa causing colitis and the capacity for further hematogenous spread causing invasive infection such as liver abscess. E. histolytica infection is more common in homosexual males. Transmission in these patients occurs by oral-genital or oral rectal practices. E. Histolytica seropositivity is higher when CD4 count is < 200/µl in patient infected with HIV. Common clinical symptoms in chronic diarrhea, dysentery, abdominal cramps, weight loss, abdominal pain, and high grade fever, abdominal tenderness is found in patient of amoebic liver abscess.

**CNS INFECTIONS:**

**CRYPTOCOCCAL MENINGITIS:** C. Neoformans is leading infectious cause of meningitis in patient with AIDS. In approximately 2% of the patient, it is the initial AIDS defining illness and generally occurs when the CD4 + count is < 100mg/µl. Presentation is mostly of sub-acute mening-encephalitis with fever, vomiting, altered sensorium, meningeal signs and headache. Focal neurological deficit and seizure incidences are low. CSF examination shows modest leucocytosis, mild protein elevation and decreased glucose level. The diagnosis is made by identification of organism in spinal fluid by India ink preparation or cryptococcal antigen detection.

Treatment is initiated with IV Amphotericin-B, at a dose of 0.7mg to 1mg/kg daily, Flucytosine 25mg/kg QID, followed by fluconazole 400mg/d PO for 10 weeks and then fluconazole, 200mg/d until CD4 + count has increased to > 200cells / µl for 6 months in response to HAART.

**TOXOPLASMOSIS:** Toxoplasmosis is among the common causes of secondary CNS infection in patient with AIDS, but its incidence is decreasing with increased coverage of HAART in the population. It is late complication of HIV infection and is usually found in patients with CD4 count less than 200cells/µl. Clinical presentation of cerebral toxoplasmosis includes fever, headache and focal neurological deficit. Patient may present with hemiparesis, aphasia or seizures. MRI findings include:

Multiple lesions at multiple locations and demonstrate ring enhancement on contrast MRI. The definitive diagnostic procedure is brain biopsy but is generally reserved for patient who fails on empirical therapy after 2-4 weeks. Standard treatment is sulfadiazine and pyremethamine with Leucovorin for minimum of 4-6weeks. Clindamycin in combination with pyrimethamine, Azithromycin plus rifabutin are alternative regimens. . Relapses are common and therefore maintenance therapy with sulfadiazine, pyrimethamine and leucovorin is recommended till the CD4 + count remain < 200cells/µl.

**CYTOMEGALOVIRUS RETINITIS:** CMV retinitis is among the most devastating consequences of advanced HIV infection. The majority of cases occurs in patients with CD4 + count < 50/µl. Patient
with CD4 + count < 100/µl should go for ophthalmologic examination every 3-6 months. CMV retinitis usually presents as a painless, progressive loss of vision. Symptoms like 'Floaters', blurred vision and scintillations are also commonly encountered. The involvement is usually bilateral although one eye is more affected than other in majority of the patients. CMV retinitis is necrotic inflammatory process and visual loss is generally irreversible.

Fundoscopic examination reveals perivascular hemorrhage and exudates in retina.28,29

Vitreous and aqueous humor sampling with molecular diagnostic techniques may be used in a patient with atypical presentation or with lack of response to treatment. Therapy for CMV retinitis consists of oral valganciclovir, I/V ganciclovir, or I/V Foscarnet with cidofovir as alternative. Ganciclovir and foscarnet in combination therapy is shown to be slightly more effective that either ganciclovir or foscarnet alone. 3 – Week induction course is followed by maintenance therapy with oral valganciclovir. Maintenance therapy is continued until CD4 + count remain > 100-150/µl for > 6 months.30

OPPORTUNISTIC INFECTION PROPHYLAXIS: Opportunistic infection prophylaxis in HIV patients is given according to CD4 levels and if the patient has an episode of OI before. Table 2 summarizes the agents used for prophylaxis and alternatives.

CARDIAC INFECTIONS AND OTHER MANIFESTATIONS: HIV / AIDS can involve all the organ system of the body and cardiovascular system is no exception. The insult to the heart can be direct (retrovirus) or indirect (due to superimposed opportunistic infections). As far as cardiovascular system is concerned it can involve all the layers of heart i.e. endocardium, myocardium, pericardium. Beside that it can involve blood vessel also especially the coronary arteries and can involve pulmonary artery leading to pulmonary arterial hypertension.

Myocardial Involvement: It is the commonest layer of heart to get affected. Its involvement is more commonly asymptomatic. Autopsy based studies have shown incidence of around 50% an all HIV / AIDS cases 31 as against Echocardiography based study by Herkowitz et.al.32 Myocardial involvement or myocarditis manifests as asymptomatic left ventricular dysfunction or as dilated cardiomyopathy (DCM).

Various factors have been attributed to the cause of myocardial dysfunction in such patients that include drugs (Zidovudine, didanosine),33 infections (viral infections like herpes simplex, cytomegalovirus, direct injury due to retrovirus per se), bacterial infections like mycobacterium tuberculosis, mycobacterium avium, fungal infections like Cryptococcus neoformans, histoplasma, parasites like toxoplasma Gondii, etc. but the paradox is that even after extensive workup including myocardial biopsies the diagnostic yield is around 20% only i.e. in 80% cases the exact diagnosis remains elusive.34

Patient with raised troponin T have poor prognosis and they need myocardial biopsy for further management.35 If the biopsy shows mitochondrial myopathy (due to zidovudine or didanosine) these drugs needs to be stopped temporarily or other drugs needs to be started.

Pericardial Involvement: Incidence wise it is next to myocardial involvement. Mild pericardial effusion is common. Massive effusion and effusion causing tamponade is rare and is limited to reports only.
The overall incidence of effusion is 11% in patients with HIV. The very onset of pericardial effusion pretends poor prognosis vis-à-vis an HIV/AIDS patient. Pericarditis can be with or without pericardial effusion. Causes include HIV itself, infection (viral, bacterial, fungal, and protozoal), enhanced cytokine expression, capillary leak syndrome, etc. Mild pericardial effusion needs to be observed and followed up.

Moderate /massive effusion which is not resolving needs to be evaluated which include Echo/Flouro guided aspiration and routine biochemical and cytology evaluation, cultures. Special investigation include PCR, ADA (Adenosine deaminase), gamma Interferon for mycobacterium tuberculosis and cell cytometry for malignancies. In a case of massive effusion and tamponade always exclude tuberculosis, Lymphoma and Kaposi’s sarcoma caused by HHV-8 virus. Definitive therapy is ART, drugs for opportunistic infection (e.g. ant tubercular Therapy for TB, Steroid is must in tuberculosis), secondary prophylaxis e.g. Septran (Co-Trimoxazole) as per CD4 count.

**Endocardial Involvement:** It can be infective or non-infective. Infective Endocarditis especially the infective is rare and is commonly seen in intravenous drug abusers. It commonly affects the right sided valves like tricuspid and pulmonary. Staphylococcus aureus and pseudomonas aeruginosa are implicated as etiology of infective endocarditis. Presentation includes right sided heart failure, pulmonary infarcts, non-resolving pneumonias.

Treatment includes cover from these organisms as well as antifungal coverage to take care of candida, aspergillus or possible Cryptococcus. Non-infective (marantic) endocarditis is due to sterile inflammation of left sided valve. It basically consists of platelets and fibrin plugs. Embolism of the vegetation is common due to friable nature and can cause stroke or peripheral gangrene.

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**TABLE 1: OPPORTUNISTIC INFECTIONS PROFILE IN INDIAN PATIENTS**

| Disease                   | Frequency   |
|---------------------------|-------------|
| Pulmonary tuberculosis    | 35-50%      |
| Oral candidiasis          | 30-40%      |
| Cryptosporidial diarrhea  | 20-40%      |
| Pneumocystis jirovecii    | 5-15%       |
| Herpes simplex            | 5-15%       |
| Herpes zoster             | 5-15%       |
| Toxoplasmosis             | 5-10%       |
| Cryptococcal meningitis   | 4-8%        |
| CMV retinitis             | 2-5%        |
TABLE 2: Opportunistic Infections prophylaxis for HIV-infected patients (OD=once daily, BD= twice daily).

| Pathogen                  | Indication                          | First choice                        | Alternatives                                                                 |
|---------------------------|-------------------------------------|-------------------------------------|------------------------------------------------------------------------------|
| *Pneumocystis jirovecii*  | CD4 count <200 cells/mm³ or oropharyngeal candidiasis | TMP-SMZ (cotrimoxazole) double-strength tablet OD | • TMP-SMZ single-strength tablet OD  
• TMP-SMZ double-strength tablet Thrice weekly  
• Dapsone 50 mg BID  
• Dapsone 100 mg OD  
• Pyrimethamine 50 mg + dapsone 50 mg + folic acid 15 mg OD  
• Pentamidine inhalation 300 mg every three weeks  
• clindamycin or atovaquone |
| *Toxoplasma gondii*, primary | CD4 count <100 cells/mm³ | TMP-SMZ double-strength tablet OD | • TMP-SMZ single-strength tablet OD  
• Dapsone 50 mg OD + pyrimethamine 50 mg once weekly + folic acid 25 mg OD |
| *Toxoplasma gondii*, secondary | CD4 count <100 cells/mm³ | TMP-SMZ double-strength tablet PO OD |  
• Dapsone 50 mg OD + pyrimethamine 50 mg OD + folic acid 15–25 mg OD |
| *M. avium complex*        | CD4 count <50 cells/mm³            | Azithromycin 1200 mg once weekly     | Clarithromycin 500 mg BID |
| *Cryptococcus neoformans* | CD4 count <50 cells/mm³            | Fluconazole 100–200 mg OD            |  

![Stages of HIV Disease](image)
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