DOI: 10.7860/NJLM/2019/39772:2337

Review Article

Microbiology Section

A Review on Respiratory Infections in HIV-Infected People

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ABSTRACT

The infectious disease which created a huge impact on mankind over the past few decades is the Acquired Immunodeficiency Syndrome (AIDS). Although the devastating nature of this syndrome is not directly due to the virus, the immune suppression that ensues triggers a cascade of opportunistic infections that can kill an individual. The process of a person acquiring Human Immunodeficiency Virus (HIV) can therefore be referred to as "Opening the Pandora`s box". The commonest system in the body prone to opportunistic infections is the respiratory system. The types of pulmonary infections in AIDS, organisms associated, clinical manifestations, diagnosis and management have been compiled for collective understanding.

Keywords: Acquired Immunodeficiency syndrome, Fungal lung diseases, HIV-related, Opportunistic infections, Parasitic pulmonary infections, Pneumocystis pneumonia

INTRODUCTION

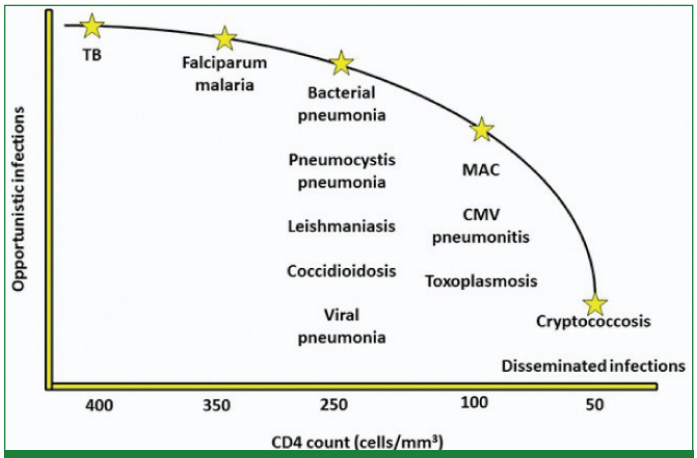
Since the discovery of HIV in 1983, it has created much interest among health care professionals due to various reasons. Major institutes have undertaken research on the pathogenesis, disease spectrum, diagnosis, treatment and prophylaxis of HIV. The targets of these researches are to discover a possible cure and vaccine for HIV, but are still in vain. Although a person infected with HIV is prone to various adverse events leading to death, one can alleviate the severity of infection with the help of prophylactic therapy [1]. For that reason, it is wise to have a knowledge on infections that can be anticipated in these individuals and when in the course of disease to anticipate them. Since the respiratory tract is prone and sensitive to microbial invasion, pulmonary infections are the commonest in a person with AIDS [2].

CD4 levels and the risk of acquiring opportunistic infections are indirectly proportional to each other [Table/Fig-1]. Pulmonary opportunistic infections are due to varied aetiological agents like bacteria, parasites, viruses and fungi [1]. A detailed review of these infections along with emerging pathogens infecting the respiratory system in people living with AIDS is explained in this review.

Infections	Organisms	CD4 count (cells/mm^3)
Bacterial	*Mycobacterium tuberculosis*	<400, disseminated TB usually at CD4 <200
	Mycobacterium avium complex	<100
	Streptococcus pneumoniae	<250
	Haemophilus influenzae	<250
	Staphylococcus aureus	<250
	Nocardia species	<250
Fungal	*Pneumocystis jirovecii*	<200
	Cryptococcus neoformans	<50
	Penicillium marneffii	<100
	Histoplasma capsulatum	<150
	Coccidioides immitis	<250
	Aspergillus species	<100
Parasitic	*Toxoplasma gondii*	50-100
	Plasmodium falciparum	<350
	Leishmania donovani	<200
Viral	Cytomegalovirus	<100
	Varicella zoster virus	<200
	Human Herpes Virus 8 (HHV 8)	<200

[Table/Fig-1]: Opportunistic pulmonary infections commonly encountered in AIDS with CD4 count [1].
*Disseminated infections usually occur when CD4 count falls below 50-100 cells/mm^3

Timeline of respiratory infections ensuing as CD4 count fall progresses is depicted in [Table/Fig-2].



[Table/Fig-2]: Relationship of pulmonary opportunistic infections with CD4 count.
TB: Tuberculosis; MAC: *Mycobacterium Avium Complex*; CMV: Cytomegalovirus

Bacterial Pulmonary Infections in HIV

1) HIV–TB co-infection: Given the fact that respiratory manifestations predominate the list of opportunistic infections in patients with HIV, Tuberculosis (TB)is the commonest and most devastating infectious disease in a HIV positive patient especially in developing nations. It has also been proven that the greatest risk of a person acquiring tuberculosis is HIV positivity, more so in endemic countries like India [3]. It is therefore wise to consider opportunistic infection with tuberculosis in HIV positive individuals and vice versa. In addition to the usual rising curve of tuberculosis incidence worldwide, the past few years have seen significant propulsion in this rise after the advent of HIV.

An estimate of over 34 million individuals was affected with HIV in a 2013 report by the World Health Organization (WHO)[4]. In 2010, the estimated prevalence of TB infected HIV patients were 14 million signifying almost 50% individuals being coinfected with TB and HIV [5]. Tuberculosis remains the forerunner leading to death of HIV infected individuals and in India, TB-HIV co-infection is reported to be around 38% [6]. An interesting fact is that people with HIV develop TB infection well before the drop of CD4 count below 400-500 is ironic [6]. Due to this reason, the WHO has recommended

antiretroviral therapy initiation for all HIV infected patients who develop tuberculosis irrespective of their CD4 count [4].

Normal individuals who are exposed to Mycobacterium tuberculosis do not develop active infection with the bacteria as the bacteria becomes latent. But this is not the case in HIV affected population wherein they are prone to development of active TB following infection in contrast with normal individuals [7]. Major studies have been conducted worldwide to answer the question: "What are the alterations that occur in a HIV infected individuals` immune system which renders them susceptible to develop active TB?" We collated few hypotheses from previously published studies as follows [8,9]:

- Primary tuberculosis or reactivation of tuberculosis occurs due to CD4 cell depletion by HIV at the site of granuloma. This also results in active replication of the virus at these sites. Studies support this hypothesis by showing a high susceptibility for tuberculosis infection in HIV patients with lower CD4 count than in those with higher CD4 count. Reduced ability of granuloma formation in HIV: Macrophages and lymphocytes are not available to contain the tubercle bacilli within granuloma. This results in rapid multiplication and dissemination of *Mycobacterium tuberculosis* throughout the body.
- Thymic failure results due to depletion of thymocytes, destruction of T cell precursors within the bone marrow and also the thymic epithelia. T cells become dysfunctional due to continuous stimulation resulting in imbalance of the different T cell populations.
- Alteration in functionality of macrophages and T cells is noticed in TB-HIV coinfection. Macrophages in these individuals release lesser amount of Tumour Necrosis Factor α (TNF-α) and therefore TNF induced apoptosis is compromised. This also results in active replication of HIV within these macrophages.
- Memory T cells which are specific to *M. tuberculosis* in individuals with latent tuberculosis produce lesser amounts of Interferon γ (INFγ) following HIV infection. Studies in active tuberculosis in HIV infection also have demonstrated lower levels of INFγ and IL2.

The complex pathogenicity of TB in HIV results in varied and atypical clinical features such as lower lobe involvement and diffuse infection rather than typical features of TB such as cavitation [10], basal involvement, miliary tuberculosis, hilar and mediastinal lymphadenopathy [11].

Diagnosis of pulmonary tuberculosis in HIV infected individuals becomes complicated as the bacillary load is low in pulmonary secretions [12]. Radiographic features show basal pulmonary infiltrates, miliary changes, mediastinal and hilar lymphadenopathy [11]. Central necrosis appearing on Computed Tomography (CT) as low attenuation of lymph nodes is diagnostic of tuberculosis.

2) Bacterial Pneumonias in HIV: *Mycobacterium Avium Complex* (MAC) is the commonest atypical Mycobacteria causing pulmonary infections in HIV infected individuals.The first reported case of MAC was in a miner who presented with pulmonary symptoms in USA [13]. Since the advent of AIDS, the spectrum of clinical presentation has broadened as disseminated infections are being reported. Dissemination occurs when there is a drop of CD4 count below 50 cells/mm^3 [14].

Other bacterial agents are associated with pneumonia in patients when the CD4 count dips below 200 cells/mm^3. In contrary to the notion that opportunistic infections commonly occur among AIDS patients in developing nations, bacterial pneumonias are more common in AIDS patients in developed countries [15,16]. In India, due to the burden of tuberculosis, bacterial agents are second common in causing lung infections. *Streptococcus pneumonia* followed by *Haemophilus influenzae* is the commonly associated community pathogens [17]. Rarely occurring pathogens causing community acquired pneumonia are *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia pneumophila* [17]. *Rhodococcusequi*, an unusual Gram positive cocci has also been reported in severely immunosuppressed HIV infected patients with pneumonia. *R.equi pneumonia* is characterised by cavitary upper lobe infiltrates, thereby mimicking tuberculosis. [Table/Fig-3] shows the features of common bacterial pulmonary infections in AIDS patients.

Fungal Pulmonary Infections in HIV

The first infection that triggeredsuspicion of HIV in 1983 was a fungal agent *Pneumocystis jirovecii* among homosexual men in Los Angeles, USA. The reason behind the discovery of HIV was pneumonia occurring due to *Pneumocystis jirovecii*. Having said that, the importance of fungal opportunistic infections in HIV is highlighted. Around 90% *Pneumocystis Jiroveciipneumonia* (PJP) are seen in patients having CD4 counts less than 200 cells/mm^3. Other contributing risk factors for development of PJP include oral thrush, previous exposure to Pneumocystis jirovecii, higher plasma

Organism	Cumulative incidence	Clinical features	Laboratory findings/diagnosis	Imaging features
Mycobacterium avium complex [13]	20% of Mycobacteriosis	Pneumonitis, pre tracheal lymphadenopathy	Anemia, elevated alkaline phosphatase, isolation from culture, DNA probes, acid fast stain	Cavitary infiltrate involving the apical and anterior segments of the upper lobes, diffuse interstitial or reticulonodular infiltrates, solitary pulmonary nodule
Streptococcus pneumoniae	70% of bacterial pneumonia	Acute onset of fever, breathlessness, productive cough, chest pain, chills, tachypnea, decreased oxygen saturation, progression to sepsis.	Leucocytosis with left shift, Gram stain, blood culture, urine antigen detection, PCR	Unilateral focal, segmental or lobar consolidation, pleural effusion
Haemophilus influenzae	10% of bacterial pneumonia	Fever, chills, cough with expectoration, tachycardia, pleuritic chest pain, decreased oxygen saturation, progression to sepsis.	Leucocytosis with left shift, Gram stain, blood culture, PCR for nucleic acid detection	Unilateral focal, segmental or lobar consolidation, pleural effusion
Staphylococcus aureus	9% of bacterial pneumonia	Fever with chills, productive cough, chest pain	Gram stain, culture, PCR for nucleic acid detection	Cavitation, parenchymal necrosis
Nocardia species		Nonspecific respiratory features, Lung abscess	Gram stain, culture, modified acid fast stain	Focal infiltrates, Lung abscess
Legionella pneumophila	6% of bacterial pneumonia	Pleural effusion, fever, signs of pneumonia	Urine antigen detection, PCR for nucleic acid detection, culture, direct fluorescent antibody detection from lung tissue	Focal alveolar infiltrates
Mycoplasma pneumonia and *Chlamydia pneumophila* (TWAR agent)		Bronchitis, atypical pneumonia	Giemsa stain, direct immunofluorescence, culture in embryonated egg, cell lines, ELISA, PCR	Ground glass infiltrates, pleural effusion, mediastinal lymphadenopathy

[Table/Fig-3]: Features of bacterial pulmonary infections in AIDS patients [13,15].
PCR: Polymerase Chain Reaction; ELISA: Enzyme Linked Immuno Sorbent Assay; TWAR: Taiwan Acute Respiratory Agent

level of HIV RNA, recurrent bacterial pneumonia, unintentional weight loss [18,19].

Other fungal pathogens associated with pulmonary infections in AIDS depend on the geographic distribution and endemicity of the fungi. *Histoplasma capsulatum* and *Coccidioides immitis* commonly occur in south-central America, Ohio and Mississippi river valleys. *Cryptococcus neoformans* is worldwide in distribution; however certain species of Cryptococcus like *C.gattii* are prevalent in Australia, subtropical countries and north-west Pacific regions [1].*Penicillium marneffeiis* predominantly distributed in Southeast Asian countries like Thailand, Taiwan, India, Vietnam, Hong Kong, Southern China, Laos [20]. In India, common fungi isolated from lungs of HIV infected individuals are: *Pneumocystis jirovecii*, *Aspergillus*, *Cryptococcus* and *Candida* [21]. The underlying risk factor for acquiring fungal pulmonary infections like Penicilliosis and Histoplasmosis has been reported to be Tuberculosis. PJP is known to be an underlying trigger for pulmonary Aspergillosis in AIDS patients [21]. [Table/Fig-4] illustrates the common fungal infections in AIDS patients.

Fungi	Clinical features	Laboratory diagnosis	Radiological findings
Pneumocystis jirovecii	Fever, non-productive cough, dyspnea, inspiratory crackles	Induced sputum/ BAL should be collected for Toluidine blue stain, PCR	Reticular or granular infiltrates (initially perihilar region, progresses to diffuse distribution), ground glass opacities. Rarely : intrathoracic adenopathy, pleural effusion
Penicillium marneffii [20]	Productive cough, dyspnea, hemoptysis	Cytology or biopsy specimens for periodic acid Schiff, methenamine silver stains, culture, PCR	Diffuse reticular/ localized infiltration or cavitary lesion
Cryptococcus neoformans [22,23]	Pleuritic chest pain, fever, cough, hemoptysis, respiratory distress	India ink stain, H&E stain, PAS, GMS stain, culture, antigen detection by latex agglutination, PCR	Nodular lesions (solitary nodule), cavitations, pleural effusion, pneumonic infiltrates
Histoplasma capsulatum [24]	Fever, cough, dyspnea, dissemination leading to shock	PAS, GMS stain, culture, Enzyme Immunoassay, DNA probe, PCR, LAMP assay	Reticular or granular infiltrates, nodules, intrathoracic adenopathy
Coccidioides immitis [25]	Fever, cough, dyspnea, chest pain	PAS, GMS stain, culture, Enzyme Immunoassay, DNA probe, PCR, Immunoglobulin M	Diffuse reticulonodular infiltrates, cavities, nodules, pleural effusion, respiratory failure
Aspergillus species (Allergic bronchopulmonary Aspergillosis, Aspergilloma) [26]	Fever, cough, dyspnea, chest pain, hemoptysis	KOH, culture, Galactomannan antigen detection by ELISA, PCR	Thick walled cavities in upper lobe, hazy infiltrates with segmental lobar atelectasis

[Table/Fig-4]: Features of Fungal Pulmonary Infections in AIDS patients [20,22-26].
PCR: Polymerase Chain Reaction; H&E: Haematoxylin and Eosin; KOH: Potassium Hydroxide; PAS: Periodic Acid Schiff; GMS: Gomori Methenamine Silver; ELISA: Enzyme Linked Immuno Sorbent Assay; LAMP: Loop Mediated Isothermal Amplification

IV. Parasitic Pulmonary Infections in HIV

Toxoplasma gondii, *Plasmodium falciparum* and *Leishmania donovaniare* the common protozoans associated with pulmonary manifestations in AIDS patients. *Strongyloidesstercoralis* causing hyperinfection syndrome is the only helminthic infection of great concern in these patients. Association of hyperinfection syndrome with CD4 count is unpredictable [1]. Reports from various countries reveal a CD4 count widely ranging from 100-500 cells/mm^3 among patients with hyperinfection syndrome. The possible explanation could be the difference in parasitic load causing hyperinfection among infected patients [27].

Demographic distribution of parasites causing pulmonary infections is mainly in tropical and subtropical countries. All these parasites are equally found in South East Asia, Sub-Saharan Africa, South America, Mediterranean countries [27]. [Table/Fig-5] shows the parasitic pulmonary infections encountered in AIDS patients.

Parasite	Clinical features	Laboratory diagnosis	Radiological findings
Toxoplasma gondii	Influenza like illness, fever, pneumonia	Giemsa, PAS, silver stains, peroxidase stains, animal inoculation, tissue culture, immunoassays, ELISA, PCR	Interstitial pneumonia, diffuse alveolar damage, necrotizing pneumonia, obstructive or lobar pneumonia
Plasmodium falciparum	Pulmonary oedema, ARDS	Leishman`s, Giemsa stain, QBC, culture in RPMI 1640, Delbecco`s modified Eagle medium, ICT, ELISA, PCR	Diffuse interstitial and pulmonary oedema, pleural effusion, lobar consolidation, bilaterally pulmonary infiltrates, diffuse bilateral alveolar opacities, bilateral basal ground glass opacities
Leishmania donovani	Pleural effusion, mediastinal adenopathy, pneumonitis	LD bodies in Leishman, Giemsa or Wright stains, NNN medium, Schneider`s liquid medium, CFT, ELISA, IFA, ICT, PCR	Pneumonitis, pleural effusion
Strongyloidesstercoralis	Cough, hemoptysis In hyperinfection syndrome:asthma, ARDS, intra-alveolar haemorrhage	Wet mount – saline and iodine mount, entero test, agar plate culture, Harada Mori filter paper culture, ELISA, PCR	Pulmonary infiltrates, miliary nodules, airspace opacities, ARDS in severe disease, rarely granulomatous changes

[Table/Fig-5]: Features of Parasitic Pulmonary Infections in AIDS patients [27].PAS: Periodic Acid Schiff stain; PCR: Polymerase Chain Reaction; ELISA: Enzyme Linked Immuno Sorbent Assay; QBC: Quantitative Buffy Coat; RPMI: Roswell Park Memorial Institute; ICT: Immunochromatography; LD: Leishmania Donovani; NNN: Novy-McNeal-Nicolle; CFT: Complement Fixation Test; IFA: Indirect Fluorescent Antibody; ARDS: Acute Respiratory Distress Syndrome

Apart from commonly encountered parasites, rare association with pulmonary infections have been observed with *Cryptosporidium parvum*, *Microsporidium*. Focal pulmonary lesions may not be pathognomonic, however these miscellaneous parasites produce lung lesions when they get disseminated due to severe immunosuppression.

V. Viral Pulmonary Infections in HIV

Viruses contribute around 5% of pulmonary infiltrates of infectious aetiology in AIDS patients [1]. Thus, viral aetiology should be considered when an AIDS patient presents with community acquired pneumonia. Herpes group of virus {Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), Human Herpes Virus 8 (HHV8)} are common viruses causing pulmonary infection in AIDS patients[1]. With advent of newer molecular diagnostic methods, studies in the past decade have resulted in detection of various other viruses associated with pulmonary infections in AIDS patients. These newer viral agents are:Influenza virus, Respiratory Syncytial Virus(RSV), Adenovirus, Rhinovirus, Parainfluenza virus, Coronavirus, Human metapneumovirus, Human Bocavirus [28].

Herpes Viruses: In this broad group of DNA viruses, Cytomegalovirus is associated commonly with pulmonary infections. CMV infection gets reactivated and is not acquired in HIV especially when the CD4 count falls to 50 cells/mm^3 either before initiation of ART or in patients with treatment failure [29]. Most HIV patients have asymptomatic latent CMV infection which gets activated when the CD4 count falls drastically [29]. Pneumonia caused by CMV and Pneumocystis jirovecii resemble each other with clinical features of fever, cough, hypoxemia. Diffuse opacities and pleural effusion are the commonly encountered radiographic features of CMV pneumonia.

Herpes simplex virus is the next common cause of viral pneumonia in AIDS patients. Known for its latency and chronicity, HSV causes herpetic tracheobronchitis or pneumonia among these patients [30-32]. Pneumothorax, ARDS and pneumomediastinum are documented rare occurrences due to HSV [33].Although both HSV 1 and 2 are associated with pneumonia, HSV 1 has been reported more frequently than HSV 2 [34].

HHV8 is aetiologically related to AIDS-related Kaposi`s sarcoma and lymphoproliferative disorders (Castleman`s disease) [1]. Incidence of Kaposi`s sarcoma has markedly decreased after usage of Anti Retroviral Therapy (ART) in HIV patients. Probable reasons for this decline are the activity of certain drugs used in ART on HHV8 namely, Zidovudine, ganciclovir, foscarnet, and cidofovir [35]. Characteristic pulmonary manifestation of HHV 8 in HIV patients is pleural effusion. Castleman`s disease manifests as lymphadenopathy, fever, multiorgan failure [36]. The greatest risk of an HIV patient developing HHV 8 infection is a drop in CD4 count below 200 cells/mm^3. Evidence supports that early initiation of ART in these patients may prevent risk of development of HHV 8 [37].

Influenza viruses are the commonest RNA viruses causing pulmonary infections in HIV patients. These infections commonly occur during Influenza pandemics and epidemics. The severity of infection, hospitalization and mortality rate increases in immunocompromised individuals more so if the patient is not on ART [38].

Respiratory Syncytial Virus causes seasonal outbreaks and viral transmission occurs through fomites, secretions and aerosols. During winter, when the incidence is high, RSV produces nasal congestion, wheeze and dyspnea. Although this clinical presentation is similar for both non-HIV and HIV infected individuals, morbidity and mortality rates are higher in HIV positive individuals [39].

Less commonly occurring viruses causing community acquired pneumonia in HIV patients are described in [Table/Fig-6].

Virus	Type of virus	Clinical features / Radiological features
Rhinovirus	RNA virus	Pneumonia, bronchiolitis, exacerbation of asthma
Parainfluenza virus	RNA virus	Bronchitis, asthma, and pneumonia
Coronavirus	RNA virus	Common cold, LRI with respiratory distress CT chest: Diffuse pulmonary ground-glass opacities
Adenovirus	DNA virus	Fever, cough, wheeze, dyspnea CT chest: Patchy and irregular or reticular opacities, consolidations
Human Metapneumovirus	RNA virus	Mild respiratory symptoms to severe bronchiolitis and pneumonia CT chest: Bilateral alveolar opacities, nodular opacities and pleural effusion
Human bocavirus	DNA virus	Clinical features not well defined. Mild to severe upper respiratory tract infections

[Table/Fig-6]: Viruses Causing Respiratory Infections in AIDS Patients [28].

VI. Treatment Guidelines for Managing HIV

The National AIDS Control Organization (NACO) has given detailed guidelines for diagnosis as well as treatment of patients with AIDS [40,41].WHO clinical staging of HIV/AIDS forms the base for ART initiation. Respiratory infections under each clinical stage are described in [Table/Fig-7].

Clinical Stage 2
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Clinical Stage 3
Pulmonary tuberculosis Severe bacterial pneumonia
Clinical Stage 4
Recurrent severe bacterial pneumonia Pneumocystis pneumonia Candidiasis of trachea, bronchi or lungs) Kaposi sarcoma Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis)

[Table/Fig-7]: Pulmonary infections under WHO clinical staging of HIV [40].

According to these guidelines, ART is initiated based on which clinical stage of HIV the patient is diagnosed with. Patients with clinical stage I and II are started on ART when their CD4 count is ≤500 [41]. Whereas, patients with stage III and IV of HIV should be started on ART irrespective of their CD4 count. For patients with TB-HIV co-infection, irrespective of their CD4 count, start ATT first and initiate ART as early as possible within 2 weeks to 2 months. However in TB-HIV co-infected patients with CD4 counts below 50 cells/mm^3, ART might be initiated simultaneously with ATT with strict clinical and laboratory monitoring [41].

CD4 counts should be monitored when initiating ART and follow up be done as follows [42]: CD4 count of any value on ART:Follow up CD4 every 6 months CD4 count between 350 - 500 on ART: Repeat CD4 at 3 months [42]

CD4 count >500 and not on ART: Repeat CD4 at 6 months Prophylaxis of opportunistic infections is provided with co-trimoxazole under the national program. Two scenarios under which this prophylaxis is initiated are:WHO clinical stage 3 or 4 patients irrespective of CD4 count, HIV infected adults with CD4 count <250 cells/mm^3.

Co-trimoxazole prophylaxis is given as a target for Pneumocystis jirovecii pneumonia,Toxoplasmosis, pathogens causing diarrhea in AIDS patients.Evidences exist to show that co-trimoxazole prophylaxis decreases mortality and morbidity in HIV infected patients [41,42]. This prophylaxis can be discontinued if the CD4 count increases twice consecutively to be >250 cells/mm^3 [41].

VII. Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV and the respiratory tract

IRIS is defined as a clinical entity wherein a paradoxical clinical worsening occurs to a new or already existing condition after initiation of ART in HIV patients [43].The synonyms given to IRIS are:Immune Restoration Disease (IRD) and paradoxical reactions. Aetiology of IRIS can be classified into infectious and non-infectious aetiologies[44]. Among infectious agents predisposing to IRIS, respiratory pathogens involved are: Mycobacterium tuberculosis (commonest), Mycobacterium avium complex,Herpes viruses (HSV, HZV, CMV), Cryptococcus neoformans, Pneumocystis jirovecii, Strongyloidesstercoralis.Incidence of IRIS has been reported to be ranging from 11-43% in Europe and USA, 41% from Africa, less than 15.2% in India [44].

Major and minor criteria for diagnosing IRIS according to French MA et al.,are [45]: Major criteria-Patients responding to ART presenting with atypical presentation of “opportunistic infections” and significant decrease of plasma HIV RNA levels.

Minor criteria-Increase in CD4 count after initiating HAART, spontaneous resolution of disease on continuation of ART but without specific antimicrobial therapy, increase in pathogen specific immune response (e.g., Delayed response in Tuberculosis).

TB-IRIS: TB-IRIS is the term given to abnormal, exaggerated immune response against alive or dead *Mycobacterium tuberculosis* bacilli in either HIV-infected (after initiation of ART) or rarely in HIV uninfected patients. Since TB-IRIS may be confused with treatment

failure, superimposed infections, treatment failure or drug resistant TB, diagnostic criteria should be applied to detect the same [46]. TB-IRIS is mainly diagnosed based on newly evolving parenchymal lesions, new lymphadenopathy, new or increased pleural effusion.

Paradoxical or unmasking are the two types of TB-IRIS. Paradoxical IRIS is defined as new/recurrent/worsening symptoms of a treated case. Unmasking IRIS is an inflammatory manifestation of a subclinical infection which is ART associated. In unmasking, unapparent signs and symptoms presentprior to initiation of ART become apparent during ART [47].

Treatment of TB-IRIS depends on the severity and presentation. Anti-TB drug initiation in most patients results in good response as most patients have non-life threatening presentations. Corticosteroids and NSAID administration is essential in few cases where the pathology is an inflammatory one such as acute renal failure, ARDS, tracheal compression due to lymphadenopathy.In these kind of life threatening situations, discontinuation of ART may be considered, however not necessary.

Among the atypical Mycobacteria, MAC is the commonest and presents with lymphadenitis, abscess formation [47].Treatment is similar to TB-IRIS with occasional requirement for excision of enlarged lymph nodes.

Pneumocystis jirovecii pneumonia IRIS may present with worsening respiratory distress, high fever in those improving with treatment. Worsening chest radiograph findings, hypoxia and fatal acute respiratory failure might occur in few patients [48].

It is necessary to be cautious and anticipate IRIS in patients undergoing treatment for specific pathogens and on ART. Appropriate use of corticosteroids, NSAIDs, ART tailoring in these patients with IRIS is necessary for better patient outcomes.

VIII. The Human Respiratory Microbiome in HIVInfection

Microbiota/normal flora refers to the assemblage/community of microorganisms present in a defined environment whereas, microbiome refers to this entire community of microbiota along with their genome [49]. The five phyla which constitute the human microbiome are: Actinobacteria, Firmicutes, Bacterioidetes, Proteobacteria, Fusobacteria. With evolving research and continuous efforts to understand human microbiome and its relationship in health and disease, HIV has become a favourite research topic for molecular biologists.

One of the first studies on lung microbiome was done to evaluate the difference between that in HIV infected and HIV uninfected individuals with pneumonia. Findings showed that there was an increase in Actinobacteria, Bacteroidetes, and Firmicutes in the HIV-infected patients and Proteobacteria predominated in the uninfected patients [50]. A significant increase in Prevotella was seen in the HIV-infected population. This finding was repeatedly observed in other studies as well [51].

In clinically asymptomatic HIV infected individuals, there was presence of Tropherymawhippleiin the lung microbiome. This organism is associated with the gut, but its presence in the lung of HIV infected individuals portrays a migration of gut microbiota to the lungs suggesting a pulmonary immunodeficiency[52].In untreated HIV infected individuals, Streptococcus was significantly high in the lungs. This is consistent with high incidence of Streptococcal pneumonia in HIV patients [53]. There is major heterogenicity in untreated HIV infected individuals which markedly reduces after treatment [54]. Based on these findings on lung microbiome in HIV, an early initiation of ART can improve prognosis and prevent chronic lung inflammation as well as opportunistic lung infections in HIV infected individuals [55]. Continuing research on this field shouldhelp in characterisation of respiratory microbiome of HIV infected individuals based on which treatment can be initiated and monitored.

CONCLUSION

Existing evidence based information on various pulmonary infections in HIV patients has been collated and detailed in this review. When treating patients with HIV, it is mandatory to anticipate opportunistic pulmonary infections based on their CD4 counts. With this comprehensive knowledge along with awareness on national guidelines for treatment of these infections, effectiveness of ART can be improved and complications can be prevented. All these can ensure better outcome, prognosis and improve quality of life in patients living with HIV.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 27, 2018**
Date of Peer Review: **Oct 12, 2018**
Date of Acceptance: **Nov 16, 2018**
Date of Publishing: **Jan 01, 2019**