The prolonged course of human immunodeficiency virus (HIV) infection is marked by a decrease in the number of circulating CD4+ T helper cells and persistent viral replication, resulting in immunologic decline and death from opportunistic infections and neoplasms\(^1,2\). Acute HIV infection is characterized by a rapid rise in plasma viraemia with a concomitant drop in CD4 count within 3-6 wk of exposure (Fig.1). Associated symptoms with this initial stage of infection occur to varying degrees of severity and may include fever, sore throat, skin rash, lymphadenopathy, splenomegaly, myalgia, arthritis, and, less often, meningitis\(^3\). The acute phase is followed by a clinically latent period with low level viral replication and a gradual fall in CD4 count where the patient can remain asymptomatic for several months to years. Mean duration of survival after diagnosis with HIV in India is 92 months\(^4\).

Median time for progression from HIV infection to acquired immunodeficiency syndrome (AIDS) was 7.9 yr in one study of patients from Mumbai\(^5\). This number is subject to a reporting bias given that fewer than 10 per cent of AIDS cases in India have been reported. With CD4 counts less than 200 cells/µl, patients are at high risk for developing opportunistic infections (OIs) like tuberculosis (TB), *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis, and cryptococcal meningitis (Fig.2). Before the availability of antiretroviral therapy, median survival after diagnosis of AIDS was 12 to 18 months\(^6\). This has changed dramatically since the advent of highly active
antiretroviral therapy (HAART) in the developed world and generic HAART in the developing world (Kumarasamy N, unpublished observation).

Specific AIDS-defining illnesses, CD4 counts, and HIV RNA levels predict survival of patients with HIV infection. Disease progression correlates with clinical features such as chronic fever, persistent cough for >1 month, chronic diarrhoea, oral candidiasis, severe chronic herpes simplex virus (HSV) infection, >10 per cent loss of body weight within 1 month, and incident tuberculosis. Generalized lymphadenopathy and herpes zoster (shingles) can occur early in the course of illness and do not correlate with more rapid progression. Patients with CD4 counts less that 200 cells/µl are 19 times more likely to die than those with CD4 counts greater than 350 cells/µl.

Clinical course and pattern of opportunistic infections varies from patient to patient and from country to country. For example, TB is the most common OI in HIV patients in India, whereas OIs like Mycobacterium avium complex (MAC) and Kaposi’s sarcoma, frequently reported in the developed world, are not as commonly reported in India. The progression and outcome of HIV/AIDS is influenced by factors such as baseline health and nutritional status, environment, endemic diseases, and access to therapy. It is important to understand the presentation of HIV disease in the local context. In this review the clinical profile of HIV disease in India is discussed through an organ-system based approach.

Pulmonary manifestations of HIV

Pulmonary diseases associated with HIV are among the most common and some of the most serious presenting illnesses in HIV-infected individuals. This section addresses some common pulmonary disease such as TB, PCP, and bacterial pneumonia.

Tuberculosis: HIV-TB co-infection is a serious problem worldwide, but especially of concern in India where background rates of TB are the highest in the world. Prevalence of HIV among patients with radiologic or bacteriologic confirmation of TB in India ranges from 2.8 to 9.4 per cent. These numbers reflect a rise in co-infection rates over the last decade. In India, the most common opportunistic infection among people with HIV infection is pulmonary tuberculosis. Understanding HIV-TB co-infection is of great importance because of increasing prevalence of co-infection, severity of clinical presentation of TB in HIV-positive patients, rapid progression of HIV disease in TB patients, and challenges in treatment of co-infected patients given possibility of drug interactions and immune reconstitution syndrome.

The risk of developing TB after an infectious contact is 5-10 per cent per year among HIV infected individuals compared to 5-10 per cent during the lifetime of HIV-negative individuals. Unlike cryptococcal meningitis or toxoplasmosis, which occur at very low CD4 counts, TB is unique in that it can occur over a wide range of CD4 counts, although it is more frequent at CD4 counts <300 cells/µl.

The clinical and radiological presentation of TB in HIV patients differs according to the degree of immunosuppression. The typical presentation of cough, sputum, dyspnoea, fever, and weight loss with apical lobe infiltrates or cavitary lesions on chest radiograph might only be seen in patients with very high CD4 counts whose immune systems are more comparable to HIV-uninfected individuals. TB in HIV patients with CD4 counts less than 300 cells/µl can present in an atypical pattern. Radiographic studies may show middle and lower lobe infiltrates, miliary TB, tubercular pneumonia, and hilar or mediastinal lymphadenopathy. Chest radiographs can also be normal in immunocompromised patients despite presence of Mycobacterium tuberculosis in sputum.

Extra-pulmonary tubercular manifestations occur in 46 to 79 per cent of patients with pulmonary TB and HIV, and is more frequent in severely immunocompromised patients. Extra-pulmonary TB has been reported in many organs: lymph nodes (most common), spleen, liver, bone, bone marrow, heart, central nervous system, gastrointestinal tract, kidneys, adrenals, thyroid, and prostate. The resulting clinical conditions include persistent fever, pleural and
pericardial effusions, ascites, pancreatitis, back pain, anaemia, mental status abnormalities, and renal failure, among others. In one study in India, extrapulmonary TB was the cause of 69 per cent of previously unexplained prolonged fever in 100 HIV-positive patients. In another study, severe weight loss in HIV patients, defined as loss of greater than 10 per cent of body weight in one month, significantly correlated with diagnoses of pulmonary and extrapulmonary tuberculosis (relative risk: 17.7). Mantoux skin testing for TB in HIV patients is challenging because results depend on the patient’s immune status. Tuberculin positivity is less prevalent among HIV seropositive patients as compared to HIV seronegative patients (22.6% vs 76.4%; P < 0.001) due to anergy resulting from immunosuppression. Therefore, results of skin testing in HIV patients should be interpreted with caution. Sputum smear positivity among HIV/TB co-infected patients has been reported in 21 to 83 per cent of patients; there was no statistically significant difference in these rates between HIV-positive and -negative patients.

Just as HIV infection can contribute to the severity of TB, there is increasing evidence that TB can affect HIV disease progression. Patients with active TB were found to have higher HIV plasma viral loads (PVLs) than asymptomatic patients with HIV and those with OIs other than TB. Pro-inflammatory cytokine production, particularly TNF-α, by tuberculous granulomas is thought to contribute to HIV viral replication. The risk of death in a cohort of Indian HIV-infected patients with TB was 3.5 times greater than the risk in HIV infected patients without TB with matched CD4 counts. Most of these deaths were caused by disease progression rather than TB itself.

Given the mortality and morbidity caused by TB, it is extremely crucial to treat TB appropriately in HIV-infected patients. HIV-infected patients respond as well as HIV-negative patients and can be similarly treated. If the patient does not respond to standard regimens, it is important to consider multidrug resistant TB. Liver function and inflammation should be carefully monitored.

Physicians should also be aware of immune reconstitution syndrome (IRS), which is described as a paradoxical worsening of clinical status after initiation of HAART in a patient with an active opportunistic infection such as TB. The incidence
of IRS among HIV/TB co-infected southern Indian patients was 7.3 per cent. It is important to continue TB treatment and give supportive therapy to patients with IRS. Current World Health Organization (WHO) guidelines recommend starting HAART between two weeks and two months after initiating TB treatment in patients with a CD4 count less than 200 cells/µl. For patients with CD4 counts between 200 cells/µl and 350 cells/µl, HAART can be started after the initiation phase of TB treatment because of the utilization of rifampicin. HIV treatment can be deferred if CD4 count is greater than 350 cells/µl.

Preventive therapy for TB using isoniazid with and without other drugs among HIV-positive patients in Africa, where TB burden is also high, has been shown to be cost effective, safe, and successful at decreasing mortality. No guidelines for TB prophylaxis exist in India due to lack of data in this setting. The safety, tolerability, and efficacy of TB prophylaxis among Indian HIV-positive patients needs to be studied.

Atypical mycobacteria like *M. avium*, which is the organism responsible for causing MAC, has only been reported by a few studies from India. The reason for the low incidence of MAC in India might have to do with low background prevalence or lack of diagnostic capabilities.

**Pneumocystis jirovecii pneumonia (PCP):** *Pneumocystis jirovecii* causes severe pneumonia in patients with AIDS. Occurrence of PCP establishes the diagnosis of AIDS and it is the most common AIDS-defining illness in the developed world. In India, however, very low rates (0.7 to 7%) of PCP have been reported. Some reasons for this could be the predominance of other pulmonary diseases like TB, and due to underdiagnosis of incident cases. PCP occurs in patients with CD4 counts under 200 cells/µl; studies from Delhi and Chennai reported median CD4 counts of patients with PCP of 142 and 87 cells/µl respectively. According to a large natural history study, Indian patients with PCP were 4.5 times more likely to die than patients without PCP. Median survival after diagnosis of PCP in this study was 24 months.

In the Indian context, PCP can simultaneously occur with other pulmonary infections, including TB, cryptococcosis, and cytomegalovirus. A case report from Pondicherry describes a patient who presented with clinical and radiologic evidence that suggested TB, was treated without response, and was found to have PCP on autopsy. Therefore, a diagnosis of PCP must be considered in patients with a diverse array of pulmonary, clinical and radiological presentations. Induced sputum, with 28-55 per cent sensitivity for PCP can be used as an alternative to invasive and expensive bronchoalveolar lavage (BAL) to diagnose PCP. PCP responds to high dose co-trimaxazole. Adjuvant use of steroids in patients with hypoxaemia is important and results in decreased mortality and morbidity.

Efficacy of co-trimaxazole against PCP, toxoplasmosis, salmonellosis, *Haemophilus* infection, and staphylococcal infection in patients with HIV has been well documented. The National Institutes of Health (NIH) treatment guidelines recommend the use of co-trimaxazole prophylaxis when CD4 counts are less that 200 cells/µl. Indian patients whose CD4 counts are less than 200 cells/µl have a 3-fold increased risk of death if they are not on cotrimaxazole prophylaxis. WHO/UNAIDS recommends use of cotrimaxazole prophylaxis in HIV-positive adults with CD4 counts less than 500 cells/µl in Africa but prospective trials in Indian patients are needed to help develop guidelines for clinical practice in our setting. Given its efficacy and affordability, co-trimaxazole prophylaxis is an important consideration in the management of HIV. Physicians should be aware of the possibility of hypersensitivity reaction (usually rash and fever) to cotrimoxazole.

**Bacterial pneumonia:** Bacterial pneumonia was reported as an opportunistic infection in 1.8 per cent of a large southern Indian cohort of HIV-positive patients. Similar to HIV-negative individuals, the most common causes of acute community acquired pneumonia, are encapsulated bacteria, *Streptococcus pneumoniae* and *Haemophilus influenzae*. Rates of bacterial pneumonia can be up to 25-fold higher among HIV infected adults than in the general community, with the most significant predictor of
risk being level of immunosuppression. Although bacterial pneumonias can occur relatively early in the course of HIV, frequency of occurrence is inversely proportional to CD4 count. Incidence of serious disseminated pneumococcal infections is 100-fold more frequent in individuals with very low CD4 counts. Among others, smoking and a history of pneumonia are additional risk factors for bacterial pneumonia. Interestingly, resulting mortality in HIV-infected individuals is not significantly higher than in the general population.

Several strategies that include long-term prophylaxis with cotrimaxazole, vaccinations, and smoking cessation have been suggested to lower the risk from bacterial pneumonias. Pneumococcal vaccination prevents morbidity due to pneumococcus. Studies are needed to evaluate the potential benefit of this vaccine in Indian HIV-positive patients.

If the clinical picture and radiological evidence do not fit TB, PCP, or bacterial pneumonia, or the patient does not improve on therapy targeted at these infections, it is important to consider the possibility of cytomegalovirus (CMV) infection, cryptococcosis, aspergillosis, toxoplasmosis, *Penicillium marneffei*, Kaposi’s sarcoma, and squamous cell carcinoma, as all of them have been reported in Indian patients with HIV and severe immunosuppression.

**Oral lesions in HIV**

Ear, nose, and throat specialists, as well as dentists, can play an important role in identifying individuals infected with HIV because oral manifestations of HIV disease are common and are among the first signs of HIV infection and immunosuppression. Oral lesions are important not only in early diagnosis but also in monitoring the progress of disease. Studies show that oral lesions often co-occur with other diseases, especially pulmonary infections. For example, one study showed that 39 per cent of those with oral lesions had concurrent pulmonary TB. This underlines the importance of examination of the oral cavity for clues about the level of immunity and the overall health status of the patient.

**Oral candidiasis:** Oral candidiasis occurs frequently in individuals with HIV infection; it has been reported as the most common HIV-associated condition, occurring in up to 70 per cent of cases.
The pseudoemembranous “white patches” variant of candidiasis is associated with more severe immunosuppression than the erythematous, hyperplastic or angular chelitis types. Median CD4 counts of patients with candida ranged between 107 and 189 cells/µl in different studies. The positive predictive value of oral candidiasis for low CD4 count is greater than 75 per cent. The presence of oral candidiasis indicates the need to start PCP prophylaxis.

**Periodontal disease:** HIV infection is associated with three characteristic presentation of periodontal disease: necrotizing periodontal disease, linear gingival erythema (LGE), and exacerbated attachment loss. LGE is described by rapid loss of bone and soft tissue in clean mouths where there is very little plaque or calculus to account for the gingivitis. However, it is difficult to distinguish LGE from non-HIV-related periodontal disease when background prevalence of periodontal disease is high. Gingivitis of unspecified kind has been reported in 24 to 47 per cent of HIV positive cohorts. LGE has a 70 per cent positive predictive value for low CD4 count (CD4 <200 cells/µl).

**Oral hairy leukoplakia (OHL):** Worldwide, prevalence of OHL among HIV infected individual ranges from 0 to 26 per cent. One study in south India reported OHL in 4 per cent of 594 HIV positive individuals. In this study, median CD4 count was 129 cells/µl, and median survival after diagnosis was 41 months. The positive predictive value of OHL for low CD4 count has been reported at 66 per cent.

**Oral ulcers:** Oral ulcers in HIV can be caused by a number of infections, primarily, HSV. Background prevalence of latent HSV-1 infection in India is 78 per cent. Herpes simplex lesions are the third most common mucocutaneous lesion in HIV-infected individuals after candida and dermatophytosis. In one study, 5.7 per cent of HIV-positive individuals had active HSV ulcers (median CD4 count=219 cells/µl). Recurrent oral and genital herpes is also fairly common.

CMV can cause oral ulcers, as can tuberculosis, histoplasmosis and Cryptococcus neoformans.

Aphthous ulcers caused by unknown immunologic and virologic factors, are also common in HIV-positive individuals. It is important to distinguish infectious causes of ulcers from aphthous ulcers in order to target treatment with antimicrobials as opposed to anti-inflammatory agents.

**Oral pigmentation:** Oral pigmentation, patchy brown to brownish-black asymmetrical lesions usually greater than 1cm, which are distinctive from racial oral pigmentation, have been reported in up to 23 per cent of HIV positive individuals. The etiology of these lesions is unclear and needs investigation.

**Dermatologic conditions associated with HIV**

HIV infection is associated with several dermatologic conditions, which can be the initial presenting signs of HIV. Cutaneous manifestations can occur in up to 90 per cent of HIV-infected individuals and can be classified into five groups: infectious, auto-immune, drug-induced, HIV-related, and cutaneous malignancies. Often, these conditions present atypically, are much more severe, and need prolonged treatment in HIV infected patients than in the general population. Most dermatologic conditions are less frequent and less severe with the use of HAART.

**Infectious:** Herpes zoster can occur early in the course of HIV disease and generally precedes other skin manifestations of HIV disease. In patients with HIV, it can present with necrotizing ulcers in a multi-dermatomal pattern, can last longer than the usual 2-3 wk, and heal leaving prominent scars. A study which showed increased prevalence of herpes zoster among injection drug user in Manipur, attributed it to the newly blossoming HIV epidemic in that population. Eight per cent of patients with HIV had herpes zoster, at a median CD4 count of 250 cells/µl. There was no associated increase in mortality.

HSV-1 was described in the oral lesions. HSV 1/2 can also be found in genital and anal areas. Prevalence of HSV-2 in a high risk HIV-negative cohort attending a STD clinic in Pune was reported to be 43 per cent. This study showed that HSV infection, especially recent incident infection can
increase chances of HIV acquisition. Control of herpes in both the HIV-infected and uninfected partner might reduce the risk of transmission and acquisition of HIV.

Human papilloma virus (HPV), which causes oral, genital, and anal warts has been reported in 29 per cent of buccal mucosal cells and 63 per cent of cervical cells in female sex workers in Kolkata. As CD4 counts drop below 200 cells/µl, warts can grow rapidly and be difficult to control.

Molluscum contagiosum, characterized by pearly pink papules with central umbilications, can be a disfiguring skin infection when it occurs in a disseminated fashion in severely immunocompromised individuals. Molluscum contagiosum accounted for 14 per cent of cutaneous lesions in one histopathologic study of cutaneous lesions in Indian patients with HIV. Giant molluscum, and xerosis/acquired ichthyosis were associated with advanced HIV diseases. Disseminated Penicillium marneffei infection, which can be confused with molluscum contagiosum has been reported in Manipur. This report, along with earlier ones from the same area, established the endemicity of this organism in eastern India.

Staphylococcal skin infection is the most common cutaneous bacterial infection in HIV patients. It was reported in 1.3 per cent of 833 HIV-positive Indian patients, and occurred at a mean CD4 count of 410 cells/µl. Histoplasmosis, cryptococcosus, scabies and dermatophyte infections are also among infectious dermatopathologic conditions affecting Indian patients with HIV.

Systemic infections like syphilis and TB have dermatologic manifestations that are seen in HIV-positive individuals. In a histopathologic study of cutaneous lesions, 13 of 195 patients had cutaneous TB and 14 had syphilis. Syphilis afflicts up to 25 per cent of HIV-positive individuals, and can present in the primary stage as a chancre, in the secondary stage with mucocutaneous features and in the tertiary stage with neurologic and cardiac involvement. Standard of care is to conduct a venereal disease research laboratory (VDRL) or rapid plasma reagin (RPR) test for all patients who are HIV positive and treat if found to be reactive on a confirmatory test.

Autoimmune: Papular pruritic eruption (PPE) is a unique dermatosis associated with advanced HIV infection, characterized by sterile papules, nodules, or pustules with a hyperpigmented, urticarial appearance, and pruritis. When patients present with intractable, unexplained itching, physicians must consider a diagnosis of PPE and investigate for HIV infection.
Alopecia, vitiligo, psoriasis, eosinophillic folliculitis, and seborrhoeic dermatitis are all examples of autoimmune conditions associated with HIV. These conditions occur with greater frequency and severity in HIV-positive patients.

**Drug-induced:** With increasing affordability and accessibility of generic HAART, dermatologic conditions associated with HIV also include the spectrum of toxicities resulting from HIV therapy. While the safety, tolerability and efficacy of generic HAART regimens has been established, there are associated toxicities that can manifest cutaneously: from generalized morbilliform exanthema to severe Steven Johnson’s Syndrome (SJS). Of the 1286 patients who were on HAART at YRG CARE, 21 per cent complained of pruritis, and 11 per cent had rash, 87 per cent of these rashes were attributed to nevirapine. SJS occurred in 11 individuals, all on nevirapine. In addition to HAART, reaction to co-trimaxazole prophylaxis, which is recommended for all patients with CD4 counts below 200 cells/µl, can also present as an allergic rash.

**Cutaneous malignancies:** Cutaneous malignancies reported in Indian literature include squamous cell carcinoma, basal cell carcinoma, and Kaposi’s sarcoma. Kaposi’s sarcoma has been widely reported in the developed world and parts of Africa. However, there have been few reports of this malignancy in India. This stark difference in prevalence might be related to differences in transmission of HIV that contribute to risk of developing Kaposi’s sarcoma and low prevalence of human herpes virus-8 in India.

**Neurologic manifestations of HIV**

Neurological complications of HIV disease can be seen in 20% of outpatients in HIV clinics and almost half of HIV patients being treated as inpatients. Since many of them are caused by treatable pathogens, it is important to understand the spectrum of neurologic diseases in India. They can be categorized into opportunistic infections, malignancy, AIDS related dementia, and vasculitis/stroke.

**Opportunistic infections in central nervous system (CNS):** Cryptococcal meningitis (CM) has been reported as the most common opportunistic infection of the CNS of Indian patients with HIV. It accounted for 2-4.7 per cent of all opportunistic infections in two large HIV-positive patient cohorts in Mumbai and Chennai. In another study of 100 HIV-positive patients evaluated for neurological disorders, 37 patients had CM, 6 of them with concurrent tuberculous meningitis. In southern Indian patients, diagnosis of CM was associated with a 7-fold increase in risk of death. The median CD4 count at presentation was 91 cells/µl, with a median survival after diagnosis at 22 months. In a study that included HIV-positive and negative patients with cryptococcal infection, those with HIV infection were found to have poorer cerebrospinal fluid (CSF) cell response and higher mortality. Poor prognostic factors for CM include positive blood cultures, altered mental status, CSF antigen titre above 1:1024, positive CSF India ink smear, CSF white cell count below 20 cells/µl, and elevated CSF pressures.

Gold standard diagnosis of CM requires demonstration of organism in CSF. However, serum cryptococcal antigen can be used as a reasonable adjunct for diagnostic purposes. Treatment involves intravenous (IV) administration of amphotericin B for 2 wk of induction therapy. Risk of renal toxicity with amphotericin treatment is high. Prospective trials comparing efficacy of fluconazole and amphotericin therapy in Indian patients are needed.

Toxoplasmosis is also a common OI of the CNS. In a large south Indian cohort of HIV-positive patients, median CD4 count at time of diagnosis was 135 cells/µl. Diagnosis of toxoplasmosis was associated with a 2.6 fold increased risk of mortality. CNS toxoplasmosis was significantly associated with a complaint of headache, and accounted for 30 per cent of HIV-positive patient presenting with seizures. Neurocystocercosis, reported in 8 patients in a recent review, along with CNS lymphoma should be considered as differential diagnoses for mass occupying lesions like toxoplasmosis.

Diagnosis of toxoplasmosis is challenging because the gold standard for diagnosis involves brain biopsy.
However, diagnosis is usually based on CNS imaging studies demonstrating typical mass lesions. Serum anti-toxoplasmosis antibodies have been used as adjuncts but cannot rule in or rule out infection with certainty because of an almost 20 per cent false negative rate\textsuperscript{79}, and high baseline seroprevalence of antibodies without active encephalitis (30\% in health volunteers and 68\% in HIV positive individuals in Mumbai)\textsuperscript{80}.

Despite the prevalence of pulmonary and extra-pulmonary TB in Indian patients, TB meningitis is less common than cryptococcal meningitis and toxoplasmosis. It accounted for 18 per cent of patients with meningitis in a large cohort of patients evaluated for neurological complications\textsuperscript{70}. The course of TB meningitis in HIV patients is different from HIV-negative patients: cognitive dysfunction is more common, and pathological features demonstrate reduced and atypical inflammatory responses, and extensive vasculopathy. There is absence of or minimal meningeal enhancement and absence of communicating hydrocephalus on computed tomography (CT) scan in HIV-positive patients. As expected, mortality is higher in the HIV positive group\textsuperscript{81}.

Other CNS opportunistic infections reported in India include herpes encephalitis, fulminant pyogenic meningitis, meningococcal meningitis, acanthamoeba infection, aspergillus infection, rhizopus infection, and neurosyphilis\textsuperscript{71,72}. There have also been a few scattered cases of primary multifocal leukoencephalopathy\textsuperscript{71,77,82}. Acute Guillain-Barre-like syndrome affecting the peripheral nervous system has also been reported in India\textsuperscript{71}.

Prevalence and incidence of all CNS infections decreased after initiation of HAART in developed countries\textsuperscript{83} and we might observe similar trends as generic antiretroviral therapy becomes more widely available in India.

**Malignancy:** In Western literature, non-Hodgkins lymphoma (NHL) is the second most common HIV-related malignancy after Kaposi’s sarcoma, occurring in 2-5 per cent of AIDS patients\textsuperscript{35}. However, reports of CNS NHL in Indian patients with AIDS are few and far between. One study reported that CNS lymphoma was found in 2 per cent of Indian patients with HIV presenting with seizures\textsuperscript{84}. An autopsy study of 85 AIDS patients in Mumbai revealed no cases of CNS lymphoma\textsuperscript{76}. CNS lymphoma should still be considered as an alternative diagnosis to space occupying lesions like toxoplasmosis and TB meningitis.

**AIDS dementia complex:** Reports about AIDS dementia complex (ADC) in India are minimal. Review of literature revealed one study in Jaipur of 30 AIDS patients, 4 of whom were diagnosed with ADC\textsuperscript{85}. It is possible that ADC is under-recognized and under-reported given that it is a chronic problem without a simple diagnostic test. However, ADC is important to recognize and manage because it impacts the quality of life of patients and impinges on their ability to function and perform their daily activities of living. HAART remains the only option for management of ADC.

**Vasculitis/stroke:** Stroke in patients with AIDS can be secondary to a number of causes - haematogenous fungal infection, herpes simplex encephalitis, cerebral varicella zoster or neurosyphilis, among others. HIV infection itself can cause vascular endothelial damage, predisposing patients with advanced disease to stroke. In an autopsy study of AIDS patients, infarcts/hemorrhages were present in 15 per cent of cases\textsuperscript{76}.

**Psychiatric illnesses:** HIV/AIDS is confounded by psychiatric illnesses, both pre-existing, and ones that develop after learning of diagnosis. Pre-existing illnesses such as drug and alcohol dependence predispose patients to behaviour that puts them at risk for acquiring HIV infection. Patients with this history must be carefully counseled regarding risks of alcohol and drug use, especially in the context of HIV disease. A study that assessed HIV patients 4-6 wk after they learned of their positive status, found that 40 per cent were depressed and 36 per cent had anxiety\textsuperscript{86}. Serious suicidal intent was seen in 14 per cent. Presence of pain, concurrent alcohol abuse, poor family relations, and presence of AIDS in the spouse were significant factors associated with depression, anxiety, and suicidal ideation\textsuperscript{86}. Supportive counselling accompanying clinical care is crucial for these patients.
Gastrointestinal manifestations of HIV

Esophagitis: Esophagitis, causing dysphagia or odynophagia, is very common among patients with advanced HIV disease. The majority of patients with dysphagia or odynophagia have candidal esophagitis alone or occasionally in association with other infectious pathogens, such as CMV or HSV. It is important to treat this condition effectively because it could lead to malnutrition and further deterioration of health in an already compromised patient. When evaluating dysphagia and odynophagia, physicians should also consider HIV-unrelated conditions like gastroesophageal reflux disease and peptic ulcer disease, which are common in the Indian population.

Diarrhoeal diseases: Chronic diarrhoea is a major problem in HIV infected persons, affecting up to 76 per cent of those with AIDS. It is associated with a 3.3 fold increased risk of disease progression. In reports from north, south and east India, *Isospora belli* and *Cryptosporidium parvum* were the two most common causes of chronic diarrhoeal disease in HIV infected persons. *Blastocystis hominis*, *Strongyloides stercoralis*, *Entamoeba histolytica*, *Giardia lamblia*, enteropathogenic *Escherichia coli*, *Enterocytozoon bieneusi* and *Campylobacter jejuni* are other causative agents of diarrhoea in Indian patients with HIV. There was no geographic pattern to the frequency of organisms.

At YRG CARE, Chennai, stools of HIV-positive patients with and without diarrhoea were tested. Interestingly, *Cryptosporidium parvum* was present in 70 per cent of stools of those with diarrhoea and 66 per cent of those without diarrhoea. Those without diarrhoea had a mean CD4 count of 406 cells/µl compared to 213 cells/µl of those with diarrhoea. Cryptosporidium is endemic in the water supply in many parts of India, and the prevalence of infections and the associated morbidity point to the importance of counseling patients regarding the importance of boiling water before consumption.

Abdominal mass lesions: Abdominal mass lesions in HIV patients can be caused by abdominal tuberculosis and abdominal lymphoma. These diagnoses should both be considered in patients presenting with diarrhoea, pain, obstruction, bleeding, or perforation (which occur with luminal involvement) or dull pain in association with fevers and a rising alkaline phosphatase (in case of hepatic involvement). In one study, patients with abdominal tuberculosis had a significantly higher risk of being HIV-positive compared with those with pulmonary tuberculosis and voluntary blood donors (16.6 vs 6.9 and 1.4%, respectively).

Hepatitis B and C: Hepatitis B and C have the same risk factors for transmission as HIV. Concurrent infection with HIV and hepatitis B and/or C is of great concern in the developed world where co-infection rates are as high as 89 per cent in some cohorts. In India, rates of co-infection with HIV and hepatitis B are reported between six and 33 per cent. In a study in the eastern state of Manipur, where intravenous drug use is high, 92 per cent of HIV-positive intravenous drug users (IVDUs) were co-infected with hepatitis C. In addition, in a study of slum residents in Chennai, IVDUs were almost 28 times more likely to be HCV infected than those denying injection drug use (IDU). In a predominantly non-IVDU population, HIV-HCV co-infection rates have been reported between 4.8 and 21.4 per cent.

End-stage liver disease caused by HCV is an important cause of death among HIV patients in the United States. In India, co-infection with hepatitis C has been found to be associated with almost an 8 fold increased risk of disease progression. Compounded by the prevalence of chronic alcoholism in HIV infected persons, and hepatotoxic drugs used in the treatment of HIV disease, co-infection with hepatitis B and C are important considerations in the management of patients with HIV.

A study in south India of high risk individuals attending a HIV voluntary counselling and testing centers found the prevalence of hepatitis B and C to be 5 and 3 per cent, respectively. Because the prevalence of hepatitis B and C in HIV infected patients is generally low, routine baseline, testing for these viruses is not recommended unless the patient has a history of injection drug use, or has elevated transaminase levels.
Ocular manifestations of HIV

A variety of ocular conditions associated with AIDS in India have been reported: extensive blepharitis and spontaneous lid ulcer\(^1\), extensive molluscum contagiosum\(^2\), frosted branch angiitis due to CMV retinitis\(^3\), subretinal cysticercosis, herpes simplex keratitis\(^4\), bilateral papilloedema with cryptococcal meningitis, acute retinal necrosis syndrome\(^5\), squamous cell carcinoma, and immune recovery vitritis following treatment with protease inhibitors\(^6\).

The most common ophthalmic opportunistic infection in India is CMV retinitis, which almost always occurs in patients with CD4 counts < 50 cells/\(\mu\)l\(^1\)\(^7\),\(^8\). Variable degrees of visual loss are frequently associated with CMV retinitis and occur due to retinal necrosis, macular oedema secondary to retinitis, optic nerve involvement and retinal detachment. Less common ocular infections are Toxoplasma gondii, varicella-zoster virus, and Pneumocystis carinii\(^1\)\(^9\).

The second most common ophthalmic manifestation of HIV infection is non-infectious retinopathy (HIV retinopathy), reported in 13-15 per cent of HIV patients presenting to an ophthalmologist\(^1\)\(^7\),\(^8\). This condition, characterized by cotton wool spots, can be an early sign of HIV infection, and must be differentiated from diabetic and hypertensive retinopathy. Given the range of ocular manifestations of HIV, routine ocular examinations and screening for visual loss is recommended in patients with CD4 counts < 50 cells/\(\mu\)l.

HIV-associated malignancies

Patients with AIDS are at increased risk for developing NHL. In the first report of lymphoid malignancies in India, 24 of 30 AIDS-related malignancies were NHL\(^1\)\(^0\). The other patients were reported to have Hodgkin’s disease, and plasmacytoma\(^1\)\(^1\). There is also a report of Promyelocytic leukemia (M3) in an AIDS patient from Manipur, eastern India\(^1\)\(^1\). In addition to lymphomas, Kaposi’s sarcoma, squamous cell carcinoma, and cervical cancer are malignancies of concern in HIV-infected individuals.

Women

Among special concerns for women with HIV are recurrent vaginal candidiasis, menstrual disorders, anaemia, increased risk of cervical cancer, effects of HIV on pregnancy, and mother-to-child transmission of HIV. Cervical cancer is the most important cause of cancer-related deaths among
women in India. In Indian women, HIV infection is associated with a greater than a 2-fold risk of having an abnormal pap smear\textsuperscript{112}, which subsequently puts them at increased risk for cervical cancer. There are very few studies on HIV disease in Indian women; more studies on the clinical spectrum of HIV disease in women are needed in India.

Children

Vertical transmission is responsible for between 67 and 87 per cent of paediatric HIV infection, with the majority of the remaining infections occurring due to blood transfusions\textsuperscript{113,114}. The clinical features of HIV infection in children are different from those in adults. Perinatally infected children become symptomatic by five years of age. Failure to thrive is the most common clinical condition associated with HIV infection in children\textsuperscript{113,114}. Pulmonary and extrapulmonary tuberculosis was consistently the most frequent opportunistic infection reported in two major studies in Indian children with HIV\textsuperscript{113,114}. Although frequencies differed, oral candidiasis, hepatosplenomegaly, recurrent respiratory tract infection, Pneumocystis carinii pneumonia, chronic lung disease, persistent generalized lymphadenopathy, chronic diarrhoea, pyrexia of unknown origin, chronic hypertrophic parotitis, chronic otitis media, bacterial skin infection, and PPE have also been reported in Indian children\textsuperscript{113,114}.

A prospective study evaluating the efficacy of clinically-directed selective screening for HIV among the paediatric population found that the presence of oral candidiasis was a significant independent risk factor for predicting HIV infection; the presence of multiple clinical conditions including severe malnutrition, serious pyogenic infections, disseminated tuberculosis, chronic diarrhoea were also associated with increased risk of being HIV positive\textsuperscript{115}.

Like children in the U.S. and Europe, systemic and pulmonary findings are common in Indian children. Lymphoid interstitial pneumonitis (LIP) is a distinctive marker of paediatric HIV infection. This disease is marked by chronic progressive cough, digital clubbing, and fine reticular densities on chest X-ray without fever. LIP affects children far more often than adults and is associated with a good prognosis compared to other opportunistic infection\textsuperscript{116}. PCP however, was seen much less commonly in Indian cohorts (3.4-3.9\%)\textsuperscript{113,114} than Western cohorts where it is the most common AIDS diagnosis in infancy\textsuperscript{116}. Recurrent bacterial infection should raise suspicion for HIV infection. In addition, like children with HIV in Africa, Indian children are also afflicted by wasting, malnutrition, and chronic diarrhoeal disease, with cryptosporidium being the major causative organism. Appropriate immunizations, prophylaxis with co-trimoxazole, and preventative measures such as boiling water must be taken in order to avoid morbidity and

![Fig. 5. Reduction in death rate following HAART at the YRG Care, Chennai, India](image-url)
mortality in children. Little is known about the natural history of HIV disease in Indian children, and further research is needed.

**Changing clinical presentation of HIV in the context of HAART**

Highly active anti-retroviral therapy (HAART) has changed the face of HIV/AIDS by leading to a dramatic decrease in HIV-related morbidity and mortality among those with access to therapy\textsuperscript{117}. Until recently, HAART was not accessible to a vast majority of the 5.1 million Indians living with HIV in India\textsuperscript{118} primarily due to its high cost. However, production of anti-retroviral medications by Indian generic manufacturers in the developing world has drastically reduced the price of HAART to less than one US$/day (Rs.800/month)\textsuperscript{119}, and significantly increased access to treatment in resource-limited settings\textsuperscript{120} (Fig. 4).

In India, generic HAART has been shown to be safe, well tolerated and effective at increasing CD4 counts, and suppressing plasma viral load in patients with advanced HIV, comparable to the experience with proprietary HAART\textsuperscript{121,122}. Similar to developed countries, Indian patients on HAART are experiencing a decrease in the number of opportunistic infections, and HIV-related morbidity and mortality. At YRG CARE, Chennai, after the introduction of generic HAART, death rates fell from 25 per 100 person years in 1997 to 5 per 100 person years in 2003 (unpublished observation) (Fig.5). There was a significant decrease in the number of incident opportunistic infections, especially tuberculosis, in patients on HAART.

As data on HIV disease after the introduction of HAART become more available, descriptions of treated disease will include side effects and toxicities of therapy. An analysis of patients on HAART at YRG Care, Chennai, found that pruritis, nausea, and rash were the most common adverse events associated with HAART\textsuperscript{68}. Others included vomiting, anaemia, hepatitis, pancreatitis, peripheral neuropathy, lipoatrophy, lipodystrophy, and SJS. These toxicities were comparable to those reported with proprietary HAART in the developed world. Lipodystrophy was noted primarily in patients on stavudine-based HAART whereas hepatitis and SJS were associated with use of nevirapine. Stavudine and nevirapine-based HAART is currently the cheapest and most widely available triple drug regimen in resource limited settings. The prevalence of adverse events related to these drugs may rise as the use of antiretroviral therapy increases.

Immune reconstitution is of increasing concern in the developing world as HAART becomes more available in settings where opportunistic infections, especially TB, are abundant. The clinical presentation of IRS is an apparent clinical deterioration of the patient despite treatment. This could indicate a successful, though undesirable, effect of HAART, or instead, treatment failure and subsequent progression of the opportunistic infection.

The emergence of drug resistance is becoming a major concern as the use of generic HAART increases. Recently, a genotypic analysis of the sequences of HIV-1 from drug naïve patients in south India showed that 6 and 14 per cent of patients had mutations at nucleoside reverse transcriptase and/or non- nucleoside reverse transcriptase (NNRTI) resistance positions, respectively\textsuperscript{123}. This is especially significant because reverse transcriptase-based regimens with an NNRTI are very commonly used, and alternate protease inhibitor-based therapy remains very expensive and unaffordable to most patients. NNRTI resistance is important to consider because resistance to one NNRTI signifies resistance to every drug in that class, disqualifying the use of both efavirenz and nevirapine, the two most commonly used antiretrovirals in India.

**Conclusion**

HIV disease in India has a diverse range of manifestations in multiple organ systems. As the HIV epidemic grows, it is important for primary care physicians as well as specialists to learn to suspect and test for HIV infection. Early detection of HIV optimizes chemoprophylaxis for opportunistic infections and provides an opportunity for secondary HIV prevention. In addition, with the availability of HAART, treatment can vastly reduce morbidity and
mortality in Indian patients. In the new era of generic HAART, physicians must be trained to identify and manage the toxicities associated with HAART as well.

References


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