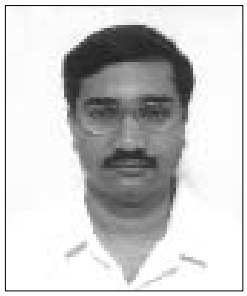

Management of Opportunistic Infections in Human Immunodeficiency Virus Infected Patients

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ABSTRACT

Opportunistic infections (OIs) are the major clinical manifestations of HIV disease and significantly contribute to morbidity and mortality amongst these patients. A variety of bacterial, viral, protozoal and fungal infections are seen in patients with HIV disease, however the commonest OI is TB. Management and prevention of OIs (chemoprophylaxis and vaccines) dramatically improve survival amongst HIV infected patients. Widespread use of Highly Active Antiretroviral Therapy (HAART) has resulted in dramatic decline in the incidence of OIs further improving survival. However, OIs occurring in presence of HAART may have altered clinical presentation and response to treatment.

INTRODUCTION

Human immunodeficiency virus (HIV) causes quantitative and qualitative dysfunction of the immune system, particularly the CD4 cells.[1] This dysfunction renders the infected patient susceptible to a plethora of opportunistic infections (OIs) and malignancies, which characterizes the symptomatic phase of HIV infection and acquired immune deficiency syndrome (AIDS). However, there has been a dramatic decline of most OIs with the advent of Highly Active Antiretroviral Therapy (HAART).[2,3] The widespread use of HAART has brought about a change in the natural history and clinical manifestations of OIs; and an improvement in the clinical outcome of many OIs. This review will focus on the management common OIs associated with HIV infection. Infection due to mycobacteria has been discussed elsewhere in this volume.

FUNGAL INFECTIONS

Candidiasis

It is the commonest cause of fungal infections in HIV infected patients. Mucocutaneous candidiasis, oral (OC), esophageal (EC) and vulvovaginal candidiasis is more common than disseminated candidiasis. Esophageal candidiasis is the commonest cause of odynophagia/dysphagia amongst HIV infected patients.[4] Topical azoles (clotrimazole troches), oral azoles (fluconazole, ketoconazole, itraconazole) or oral polyenes (nystatin, oral amphotericin B) are useful for treatment of OC.[5,6] In general fluconazole is superior to itraconazole and fluconazole and also least interacts with rifampicin, which is also concomitantly used if a patient has active TB.[7] However, unless the underlying immune suppression is corrected relapses are frequent, and occur sooner with local therapy.[6] Rarely azole resistant candidiasis may need treatment with intravenous amphotericin B. However this is used only when there has been a poor response to full doses of azoles, e.g. 800 mg/day of fluconazole.

For EC or oral intravenous azole therapy and in unresponsive infections, amphotericin B may be used. The frequency of EC as a cause of esophageal symptoms is so high that an empirical course of fluconazole is recommend for all patients presenting with these, irrespective of presence of oral candidiasis.[8] Life-long secondary prophylaxis with daily fluconazole is recommended to prevent relapses.[9] Once weekly fluconazole is no longer recommended as secondary prophylaxis.[10] However this can be safely discontinued with successful immune reconstitution with HAART.

Primary prophylaxis with azoles is not recommended because of the cost, development of resistance and/or selection of non-albicans species.

Cryptococcosis

It is common when the CD4 counts drop to less than 50/mm^3. It is the commonest cause of meningitis amongst HIV infected patients and also may present as pneumonia, lymphadenitis and unexplained fever.[11] Though the treatment of choice for cryptococcal pneumonia has not been determined through controlled trials, lifelong therapy with fluconzole 200-400 mg/day is recommended. In patients who cannot tolerate fluconazole, itraconazole is a reasonable option but ketoconazole is best avoided. In severe cases amphotericin B followed by azoles is the best choice.

The objective of treatment in cryptococcal meningitis (CM) is long-term control of infection and resolution of clinical evidence of disease and management of raised intracranial tension (ICT).[12]

Three antifungal drugs are useful in management of CM: amphotericin B, fluconazole and flucytosine. Clinical trials have demonstrated superiority of the combination of amphotericin B and flucytosine over amphotericin or fluconazole alone.[13,14] This combination was also found to have superior fungicidal activity over combinations of amphotericin with fluconazole and amphotericin with fluconazole and flucytosine.[15] Amphotericin B (0.7-1 mg/kg/day for ≥2 weeks) with flucytosine 100 mg/kg/day in four divided doses is the initial treatment of choice. Due to non-availability of flucytosine in India, monotherapy with amphotericin B is an acceptable alternative.[12] Initial therapy with fluconazole is strongly discouraged. After the 2 week induction period, induction therapy with oral fluconazole (400 mg od) for 8 weeks or until CSF cultures are sterile is recommended. Finally, lifelong maintenance therapy with fluconazole (200 mg od) is needed to prevent relapses.[16]

Amphotericin B has to be started after a test dose and gradually escalating the dose over a period of 2-3 days to the full dose. The infusions should be given in dextrose solutions only as it is unstable in saline solutions. The commonest side effects are infusion reactions (prevented by giving prophylactic antihistamines and sometimes steroids prior to the infusion), thrombophlebitis, hypokalemia, hematologic and renal toxicity (avoided by maintaining proper hydration).

Lipid preparations (liposomal Amphotericin B lipid complex, Amphotericin B colloidal dispersion) can also be used however they are more expensive.[17,18] Advantages of using these formulations are rapid achievement of full and higher doses and less toxicity. However, there is little evidence to suggest that they have superior activity over conventional preparations. Hence they may used in the following situations: intolerable adverse events like severe infusion reactions, persistent hypokalemia, renal and hematologic toxicity or in patients who may need concomitant nephrotoxic drugs e.g. streptomycin and rarely in patients with therapeutic failure with conventional amphotericin.

Management of raised ICT is crucial as it is an important contributor to morbidity and mortality in cryptococcal meningitis.[19] Elevated intracranial pressure is defined as CSF opening pressure > 200 mm H_2O measured when the patient is in lateral decubitus position.[12] Daily lumbar punctures (30 cc) is useful in reducing ICT, however a scan before is necessary to rule out any space occupying lesion. Often insertion of lumbar drain or ventriculo-peritoneal shunts needs to be performed when symptoms of raised ICT persist.[20] Use of steroids, mannitol and acetazolamide has not been shown to be effective.

Pneumocystis

Recently renamed as *P. jirovecci*, this fungus causes pneumonia (PCP) in late HIV disease (CD4<200/mm^3).[21] Although rare other extrapulmonary sites for pneumocystis include the reticulo-endothelial system, eye, thyroid and heart. Trimethoprim-sulphamethoxazole (TMP-SMX) is the initial therapy of choice.[22] The dose is 15mg/kg/day of TMP component divided at 6-8 hours intervals for a period of 14-21 days.[23] In patients intolerant to TMP-SMX, alternative therapies include: primaquine (30 mg od)-clindamycin (600 mg q6h), TMP (20 mg/kg/day)-dapsone (100 mg/day), trimetrexate (NA in India), atovaquone (NA) and intravenous or aerosolized pentamidine.[24-28] In patients with mild to moderate grade of hypersensitivity to TMP-SMX, desensitization is feasible and a useful approach.[29]

Use of steroids is recommended in patients with PCP with paO_2<70 mm Hg, or oxygen saturation less than 90% on room air, provided there are no specific contraindications (e.g. active TB or fungal infections).[30,31] Prednisone 40 mg bd for 5 days, 40 mg od for 5 days and 20 mg od until day 21 of therapy is the best choice. Steroids should be ideally initiated at the time of starting anti-PCP treatment and has very little role when initiated after 72 hours.[32] Respiratory failure when occurs may need support with mechanical ventilation.

Empirical anti-PCP therapy may be initiated in HIV-patients who present with subacute onset breathlessness with minimal clinical and radiological signs or a classical ground glass appearance on HRCT, with a CD4<200/mm^3 and not taking TMP-SMX prophylaxis. There may be occasional worsening of symptoms within 5 days of initiation of therapy but therapy should be continued for at least a period of 7 days before a determination of clinical failure is made.

After successful treatment of active disease, secondary prophylaxis is recommended until CD4 reconstitution with HAART is achieved.[33] TMP-SMX-DS 1 daily or alternate day is the most popular regime. In all HIV patients with CD4<200/mm^3 primary prophylaxis with the same drug is recommended.[33] Finally, resistance to TMP-SMX due to mutations in the dihydropteroate synthetase gene has been described although the clinical significance of the same ha yet to be determined.[34,35]

PROTOZOAL INFECTIONS

Isospora

Isospora belli is the commonest cause of chronic diarrhea, particularly in advanced HIV disease.[36] Extraintestinal isospora infection involving liver is rare. The treatment of choice is TMP-SMX (160/800 q6h for 10 days).[37] In patients hypersensitive to TMP-SMX, pyrimethamine alone (75 mg/day) may be used.[38] To prevent frequent relapses lifelong suppressive therapy with TMP-SMX (160/800mg od daily or q3w) or pyrimethamine (25 mg/day) is useful. There is no evidence to suggest that secondary prophylaxis can be discontinued when CD4 counts improve on HAART, however it may be reasonable to assume that this may be possible.

Cryptosporidia

It causes chronic diarrhea, and cholangitis. The underlying degree of immune suppression is directly related to the severity and often the unremitting nature of cryptosporidial diarrhea. Unfortunately there is no effective treatment available for controlling cryptosporidiosis. Numerous drugs have been assessed but they have been limited by small number of patients studied in non-comparative settings. Macrolides (spiramycin, azithromycin, clarithromycin and roxithromycin) is not useful for treatment.[39] Response to azithromycin has been documented in some studies, but interpretation is limited by the uncontrolled study design.[40] Paramomycin (500 mg qid) and nitazoxanide may aid some patients.[41,42] Finally, the most effective treatment is HAART, where CD4 improvements can lead to spontaneous remissions of cryptosporidial diarrhea.[43]

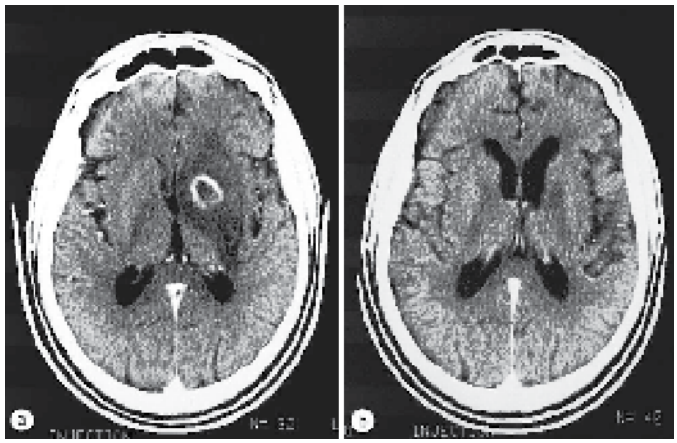

Fig. 1 : Neuroradiological resolution of toxoplasmosis a) before and b) 3 weeks after anti-toxoplasma therapy.

Toxoplasma

The commonest manifestation of toxoplasma infection in HIV infected patients is CNS toxoplasmosis where it commonly presents as focal lesions. Other extra-CNS sites for infection include eye and the lungs. Combination of pyrimethamine (75 mg/day) and sulphadiazine (4-6 g/day) is the preferred treatment choice for toxoplasmosis.[44] Folinic acid (15 mg/day) is used concomitantly to prevent bone marrow toxicity of pyrimethamine. Initial clinical response is seen within 3-7 days and radiological resolution occurs by 3 weeks (Figure). In this setting, treatment is continued for 6 weeks. Following acute therapy maintenance with the same combination (but at lower dosages) is needed to prevent relapses. With CD4 reconstitution on HAART (CD4>200/mm^3) maintenance therapy can be safely discontinued.[45]

In patients hypersensitive to sulphonamides, a combination of pyrimethamine/clindamycin can be used.[44] Alternative regime found useful for toxoplasmosis includes TMP-SMX, atovaquone, pyrimethamine/azithromycin or clarithromycin.[46-48]

In a patient presenting with a focal neurologic deficit and focal lesions in the brain, empiric anti-toxoplasma therapy is initially indicated, particularly if the patient is not taking TMP-SMX prophylaxis and has CD4< 200/mm^3.[49,50] However, this may not be true in patients responding to HAART, a biopsy of the lesion and specific therapy would be a better alternative.

Malaria

HIV infection is associated with increased frequency of clinical malaria and parasitemia particularly in advanced stages of immune suppression. There is no change in the guidelines for treatment and prevention of malaria in HIV infected patients.

Leishmaniasis

Visceral leishmaniasis (VL) is more common in HIV infected patients. The clinical criteria used to assess response to treatment are less useful and because of underlying immune deficiency relapses are very frequent. Pentavalent antimonials, amphotericin B (including lipid formulations) have been assessed in clinical trials and lead to initial clinical cure in only 65% of patients.[51-53] The total duration of therapy is 28 days. Secondary prophylaxis (Amphotericin B lipid complex 3 mg/kg every 3 weeks) may prevent relapses and whether prophylaxis can be discontinued in presence of HAART induced immune reconstitution is not known.[54] Interestingly, decline in the incidence of VL has been documented after the introduction of HAART.[55]

VIRAL INFECTIONS

Cytomegalovirus (CMV)

One of the commonest viral OI, end-organ disease usually involves the eye, lungs, Gastro-intestinal tract, and nervous system. Chorioretinitis is the commonest manifestation in the eye and is the leading cause of blindness in HIV infected patients. Treatment options for CMV infections include ganciclovir and valganciclovir, foscarnet, and cidofovir, the last two not available in India. For CMV retinitis, the location of the lesion (Zone 1, 2 and/or 3) is an important factor in determining choice of therapy.

Ganciclovir is administered intravenously in 5 mg/kg bd dose for 2-3 weeks as induction therapy.[56] Once improvement occurs life-long maintenance with 5 mg/kg od is recommended to prevent relapses. Apart from hematologic and nephrotoxicity, ganciclovir therapy is cumbersome because of the placement of intravenous catheter. An oral prodrug formulation of ganciclovir, valganciclovir (900 mg bd for 3 weeks and then 900 mg od as maintenance) is as effective in the treatment of CMV infections, particularly retinitis.[57] Oral ganciclovir (1 gm tid) is another option but it is not used during induction phase.[58] Local intraocular therapy (ganciclovir implants) is also useful for preventing relapses, with the obvious disadvantage of not covering other end organs for CMV disease for which coverage with oral ganciclovir/valganciclovir is needed.[59] Intravitreal injections of cidofovir is not recommended due to higher toxicity especially uveitis and hyptony.[60,61]

Maintenance therapy can be safely discontinued in patients with sustained increase (over 3 months) in CD4 counts>100/mm^3 on HAART.[62,63] Gancilcovir resistant CMV has been described and treated with either initiating patients on a drug from different class or using combination therapy.[64]

Varicella zoster

In HIV infected patients zoster (shingles) is the commonest dermatological complication. Antiviral therapy is indicated for all patients with zoster as soon as possible to prevent post-herpetic complications, particularly neuralgia. Acyclovir (800 mg 5 times a day for 10 days) is the treatment of choice.[65] Famciclovir (500 mg tid) is also a reasonable alternative, however it's efficacy in HIV infected patients has not been studied.[66] Valacyclovir (1 gm tid for 7 days), a prodrug of acyclovir when used in high dosages (8 grams per day) has been associated with sporadic instances of TTP/HUS in patients with advanced HIV disease.[67] Hence until further safety data is available, valacyclovir should be avoided for treatment of zoster in patients with advanced HIV disease (CD4<100/mm^3). Intravenous acyclovir is indicated for patients with primary varicella complicated with visceral involvement, ophthalmic zoster or disseminated recurrent zoster. Steroids are not recommended concomitantly in patients with zoster. Post-herpetic neuralgia can be managed symptomatically with non-narcotic analgesics, anticonvulsants, and tricyclic

antidepressants. Acyclovir resistant varicella has been reported and foscarnet is useful in treating it.[68]

JC virus

JC virus causes progressive multifocal encephalopathy (PML) commonly presenting as subacute onset focal neurologic deficit in patients with advanced HIV disease (CD4<50/mm^3). There is no specific treatment available for treatment of PML. However, patients with PML on HAART experience significantly increased survival.[69,70] Hence optimized HAART is the therapeutic strategy of choice.

Herpes simplex virus (HSV)

HIV infection is associated with increased frequency of recurrences of muco-cutaneous lesions due to HSV-1 and HSV-2.[71] Other clinical conditions due to HSV include proctitis, esophagitis and esophageal ulcers and encephalitis. Oral therapy with acyclovir, valacyclovir and famciclovir is useful in the management of muco-cutaneous HSV infections.[72] Treatment should be started as soon as the diagnosis is confirmed and continued until all lesions have crusted. In patients with disseminated muco-cutaneous lesions, herpes esophagitis and encephalitis intravenous acyclovir (10 mg/kg q8h) is recommended.[73] Recurrences of herpetic episodes are very common and secondary suppressive therapy with oral acyclovir (400 mg tds), famciclovir (500 mg bd) and valacyclovir (500 mg bd) is recommended.[72] Topical agents should not be used in HIV infected patients with muco-cutaneous herpes. Drug-resistant herpes has been documented and the treatment of choice is intravenous foscarnet.[74,75]

Hepatitis viruses

Co-infection with hepatitis viruses particularly Hepatitis B virus (HBV) and Hepatitis C virus (HCV) is very common amongst HIV infected patients. Accelerated course of hepatitis infection is common in co-infected patients. Additionally, co-infected patients have a higher risk of development of hepatitis on HAART and may also develop flaring of disease as a consequence of the immune reconstitution syndrome.[76,77]

The goal of treatment in chronic HBV infection is to prevent the development of cirrhosis. Treatment is recommended for HIV infected patients who are HBeAg positive and have evidence of liver disease (ALT > 2 times ULN or necroinflammation on biopsy) and those with HBeAg negative with an HBV DNA > 10^5 copies/ml.[78] Three currently approved drugs for treatment are interferon-alpha, lamivudine (3TC) and adefovir, the latter is not used in HIV infected patients because of the risk of development of resistance to HIV. Interferon-alpha is recommended in the dose of 5 million units SQ daily or 10 million units thrice weekly continued for 16 weeks and 12 months in patients with and without circulating HBeAg.[79] The response may be lower in HIV infected patients as compared to non-infected patients although the degree of immune suppression may play an important role in determining this.[80] PEGylated interferon is now available and is convenient to use because of it's once weekly dosing. Use of 3TC should be in combination with other antiretrovirals to prevent development of HIV resistance to this molecule.

The goal of HCV treatment is to eradicate the virus or prevent development of fibrosis when eradication is not possible. Combination treatment of PEG-IFN-alpha with ribavarin is the treatment of choice. Sustained virological response (SVR) in HIV/HCV patients may be decreased as compared to mono-HCV infected patients.[81] It is important to correct the underlying immunodeficiency with HAART before initiating anti-HCV treatment.

BACTERIAL INFECTIONS

Pneumococci

It is the commonest bacterial pathogen affecting HIV infected patients.[82] The common clinical syndromes include pneumonia, otitis media and sinusitis, meningitis and invasive pneumococcal disease. The incidence of bacteremia is higher in patients with pneumonia and blood cultures should always be sought.[83] Treatment depends on the site of infection and whether the organism is penicillin sensitive. For pneumonia the treatment of choice is penicillin, amoxycillin-clavulanate, macrolides, and clindamycin for a total duration of 10 days. For sinusitis and otitis media empiric therapy with amoxycillin-clavulanate or an oral cephalosporin is recommended.

Treponema pallidum

HIV infection may alter the natural history and response to treatment of syphilis.[84,85] The guidelines for treatment of primary, secondary and early latent syphilis amongst patients co-infected with HIV is similar to HIV negative patients. However, routine CSF evaluation is recommended before treatment of late latent syphilis and syphilis of unknown duration.[72] Benzathine penicillin (2.4 million units IM single shot) is the treatment of choice for primary, secondary and early latent syphilis. In patients who are sensitive either desensitization or doxycycline (100 mg bd for 2 weeks) is useful although no data is available on the usefulness of doxycycline in HIV infected patients. When neurosyphilis is ruled out, patients with late latent syphilis should be treated with benzathine penicillin (2.4 million units one shot weekly for 3 weeks). Finally the treatment of choice for neurosyphilis is aqueous crystalline penicillin G (2-4 million units q4h for 14 days). Procaine penicillin (2.4 million units IM daily with probenecid 500 mg q6h for 2 weeks) is a reasonable alternative.

CONCLUSION

In the absence of universal access to HAART, OIs still constitute a major problem amongst HIV infected patients. Diagnosing, managing and preventing OIs can improve survival of HIV patients. However, HAART can cause major decline in the incidence of most OIs. Additionally, HAART can also change the frequency and pattern of OIs when they do occur in spite of immune reconstitution.

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