# CURRENT THERAPY OF HIV ASSOCIATED INFECTIONS AND MALIGNANCIES

K V Ratnam, A Goh

*ABSTRACT*

***Drug therapy in AIDS is used to prolong life as there are many infections and malignancies which appear as a consequence of the immunosuppression and these can be fatal. Current anti-virals which specifically inhibit HIV replication are being used earlier to extend quality of life, maintain immune status and reduce the prevalence of opportunisitic infections and malignancies. Some infections cannot yet be treated and new therapies are awaited. It is too early in the epidemic for significant drug resistance to emerge. However, this is to be expected in the future. The prevalence of adverse drug reactions is significantly increased and therefore newer alternatives are keenly awaited. Drug treatment of HIV infected individuals is a formidable task requiring skilled multidisciplinary approach. This review summarises the most current treatment modalities for HIV associated infections and malignancies.***

***Keywords:*** *HIV, infections, malignancies, drugs.*

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## INTRODUCTION

As the human immunodeficiency virus (HIV) epidemic continues to unfold, increasing knowledge and experience of its protean manifestations has allowed more rational therapy to be used. The HIV infected individual has now more and better therapeutic options than ever before and it is likely that with the current research efforts even better options will become apparent. It is always useful to remember that the treatment of a HIV individual involves many aspects besides drugs, like staging of disease, counselling, social and family support and other issues, all of which are beyond the scope of this article. The HIV patient has from the time of infection two major problems. Firstly, treatment of the retrovirus itself and secondly, treatment of complications consequent upon virally induced immunosuppression. These complications usually fall into three big groups namely malignancies, opportunistic infections and autoimmunity. HIV gp 120 has now been shown to be critical for interaction with the CD4 (T helper) receptor[1]. With the subsequent invasion by the virus into the CD4 positive lymphocytes and macrophages, many profound changes occur in the host immune system. It is this immune malfunction that contributes greatly to the pathogenesis of Acquired Immunodeficiency Syndrome (AIDS) and AIDS related conditions[2]. However, all the observed clinical effects of the HIV infection cannot be reconciled exclusively with the direct effects of HIV on CD4 bearing cells[3]. Many of the relationships between disease and the immunological abnormalities are not known[3]. A major obstacle at present preventing scientific evaluation of drug regimes is the lack of accurate early markers of drug efficacy on HIV replication[4]. In this overview a summary of the important drugs used in management of infections and malignancies will be outlined. Drugs which have been reported to be efficacious in uncontrolled studies or isolated case reports will be omitted. Other forms of pharmacological therapy like herbs and traditional medicine will also be excluded. Many newer drugs like recombinant soluble CD4[5] and alpha interferon[5] and others are still under clinical trials either singly or in combination. There are stringent entry qualifications, entry into these trials, therefore a "parallel track" has been set up to ensure those patients that do not qualify can still obtain these drugs. Paediatric HIV infection is a specialised area which will not be covered in this overview. Generally, drugs in use for paediatric patients are similar and readers are advised to consult a more detailed review[6]. In this overview dosages of drugs will not be mentioned and readers are advised to consult a more detailed references given at the end of this article.

**National Skin Centre**
**1 Mandalay Road**
**Singapore 1130**

K V Ratnam, MBBS, MRCP (UK), MSc (Stanford), Dip Ven (Lond), FAMS
Consultant Dermatologist

**Department of STD Control**
**Blk 31 Kelantan Road**
**Singapore 0820**

A Goh, MBBS, MRCP (UK)
Medical Officer

**Correspondence to:** Dr K V Ratnam
Ratnam's Allergy and Skin Centre
#05-22 Singapore Shopping Centre
190 Clemenceau Ave
Singapore 0922.

## ANTI-VIRALS

### Zidovudine (Azidothymidine)

Inspite of considerable knowledge regarding irreversible immunodeficiency accompanying HIV infection, immunorestorative therapy has proven in the past to be disappointing[7], although more recent data suggest otherwise[8]. To date zidovudine has shown the most promise in prolonging survival and decreasing the frequency of opportunistic infections in patient with AIDS and AIDS-related complex[9]. With more than two years of use zidovudine has continued to be effective[10]. Even central nervous systems changes seem to improve with this treatment[11]. When used in HIV-infected patients with early symptoms or asymptomatic individuals with CD4 counts less than 500 cells/mm$^3$, it has also been shown to delay progression of disease[12]. The drug acts by interfering with reverse transcriptase and thereby inhibits replication of HIV[13] and terminator of DNA chain elongation. At doses of 1200 mg daily there was frequent toxicity and now with lower doses of 600 mg daily, there has been satisfactory efficacy with fewer side effects[14-16]. These preliminary data will no doubt be modified as experience increases with new dosage regimes. The most serious dose related side effect has been anaemia which frequently requires transfusion. Erythropoetin[17] infusions have helped decrease this requirement. It is possible that the incidence of this complication can be reduced by concurrent use of agents like ganciclovir and dapsone[18]. Cost has to date been a major problem especially in developing countries. Drug resistance has been described in a small number of patients[19], and it was noted that drug resistance to zidovudine emerged fairly rapidly and consistently especially in the late stages of the disease (89%) compared to early stage diseases (31%) in a 12-month study[20]. This was noticed more

commonly with high dose (1200 mg to 1500 mg) than low dose (400 mg to 600 mg) regimes[20]. This problem will require close surveillance especially now that the drug is being administered to asymptomatic patients. More recently, studies of European-Australian Collaborative Trial revealed that there was decreased disease progression and good tolerability in patients on 500 mg BID dosage of zidovudine[21]. The Veterans Administration study compared the early and late treatment with zidovudine and showed that there was indeed delayed progression to AIDS in the early intervention group, but with the onset of AIDS there was no difference in survival rates[22]. Recently, much controversy arose from the preliminary results of the Concorde Study which showed that after 3 years of follow-up in 1,749 patients, there was essentially no difference in disease progression or mortality by being on early zidovudine therapy.

This study also questioned the significance of CD4 as a surrogate marker for monitoring disease progression and assessing drug efficacy[23]. Although a controversial subject, zidovudine prophylaxis after occupational exposure may be effective if started within hours after exposure[24].

### Dideoxyinosine and Dideoxycytidine

These are newer drugs with smaller number of published clinical trials. They are particularly useful when bone marrow toxicity is a limiting factor as they are less marrow toxic[25]. Dideoxyinosine (200 to 600 mg/day) has also been shown to be useful in cases where zidovudine resistance is a problem[26]. Currently, several multicentre trials are underway to establish optional dosage regimes possibly in combination with zidovudine[27]. Didanosine$^{R}$ (dideoxyinosine) was studied with zidovudine, where patients who switched to didanosine did better than those on zidovudine (after 16 weeks of initial zidovudine)[28]. Similarly, combination dideoxycytidine (1.125 to 2.25 mg/day) with zidovudine in Phase I/II trials was found to be superior to monotherapy with zidovudine[29].

Newer reverse transcriptase (RT) inhibitors are now on trial eg D4T and 3TC. Both drugs can cause peripheral neuropathy which can be severe enough to limit their use. Dideoxyinosine is also known to induce pancreatitis and mental symptoms such as confusion[14]. There is now a general agreement that combination therapy is superior to monotherapy[30].

Recently, Phase I trials have been started for convergent therapy using zidovudine plus ddl plus pyridonone or nevirapine which in-vitro had shown the ability to mutate HIV (codon 215, 219, 74, 103) to a non-infectious entity[31].

## INFECTIONS

An increasing variety of parasitic, fungal, bacterial, spirochaetal and viral infections are being described. The observed frequency of infection depends on the prevalence of infection within the local population. Many infections are rarely single and frequently a poor clinical response to treatment may result as a consequence of a concomitant second infection[32]. Most infections are rarely completely curable and therefore usually require suppressive therapy immediately after the acute episode has subsided. This is then called maintenance therapy and contrasts with secondary prophylaxis where treatment is commenced after an interval (within months) of an acute episodes.

Another general feature is the strikingly high incidence of adverse drug reactions[32]. Another potential problem in drug therapy includes drug resistance which fortunately has not appeared to be of great consequence. Drug interactions must constantly be borne in mind as the AIDS patient is usually on several medications concurrently. Route of administration is important to ensure compliance which may be difficult to ensure with the onset of HIV encephalopathy. Since HIV infected patients require to take medications for life, frequency of administration is important to ensure efficacy. A summary of the serious infections and their treatment is given on Table I.

**Table I – Drugs used in 1993 to treat opportunistic infections occurring in HIV infected patients**

| Infections | Treatment |
|---|---|
| (A) Infections Associated with T Cells Defects | |
| **Parasites** | |
| *Pneumocystis carinii* | TMP-SMX, Pentamidine |
| *Toxoplasma gondii* | Pyrimethamine, Sulphadiazine, |
| *Cryptosporidia* | Clindamycin, Azithromycin |
| *Isospora belli* | No effective therapy? spiramycin |
| *Strongyloides stercoralis* | ?TMP-SMX |
| *Microsporidia* | Thiabendazole |
| | Albendazole |
| | Amikacin, Rifampicin, |
| | Clofazamine, Ethambutol |
| | Clarithromycin, Azithromycin |
| | Rifabutin |
| **Bacteria** | |
| *Mycobacterium avium intracellulare (MAC)* | Isoniazid, Rifamipicin Pyrazinamide, Ethambutol |
| *Mycobacterium tuberculosis (non-multidrug resistant TB)* | TMP-SMX, Ampicillin, Ciprofloxacin, Erythromycin, Rifampicin Sulphadiazine, Minocycline Ampicillin, Quinolones |
| **Fungi** | |
| *Candida albicans* | Ketoconazole, Fluconazole, Itraconazole |
| *Cryptococcus neoformans* | Amphotericin, Fluconazole |
| *Histoplasma capsulatum* | Amphotericin B |
| *Coccidioides immitis* | Amphotericin B |
| **Viruses** | |
| *Cytomegalovirus* | Ganciclovir, Foscarnet |
| *Herpes simplex virus* | Acyclovir, Foscarnet |
| *Varicella Zoster virus* | Acyclovir |
| *JC (papovavirus)* | No effective treatment |
| (B) Infections Associated with B Cells Defects | |
| *Treponema pallidum* | Penicillin |
| *Streptococcus pneumonia* | Cephalosporin |
| *Haemophilus influenza* | Gamma globulin |
| *Bramanhella lateralis* | Gamma globulin |
| *Staphylococcus aureus* | Cephalosporin, gentamicin |
| *Pseudomonas* | Gentamicin, Cephalosporin |

### Protozoan Infection

One of the commonest protozoan infection is *pneumocystis carinii* pneumonia (PCP) and it has been estimated that more than 60% of patients[33] with AIDS will acquire it, and after establishing the diagnosis, treatment is initiated with pentamidine isethionate or trimethoprim sulphamethoxazone (tmp-smx). Although the efficacy of these two drugs is similar there is good chance of response during the first episode of infection[34]. A slow initial response is to be expected accompanied possibly by drug toxicity[35,36].

Severe PCP with $PaO_2$ <70 mmHg are best treated with trimethoprim – sulphamethoxazone (tmp-smx) as first line. Trimethoprim (20 mg/kg) and intravenous pentamidine (4 mg/kg/day) is a viable second line[37]. Newer forms of therapy are being developed like trimetrexate[38] which offer satisfactory alternative to the problematic patient and is used mostly as salvage therapy. Suppressive therapy is almost always necessary after treatment and could include various regimes like aerosolised pentamidine, fansidar, dapsone or tmp-smx[32]. There is good evidence recently to justify the use of tailing doses of

corticosteroids in moderate or severe pneumocystis penumonia[39]. BW 566 C80 (Atovaquone)$^{R}$ had shown in vitro promises but is however less efficacious than tmp-smx in human trials[40].

A common cause of focal encephalitis is *Toxoplasma gondii*[41]. Therapy with pyrimethamine and sulphadiazine (pm-sdz) is usually effective[42], although several newer drugs are being evaluated. Recently, a comparative study between pyrimethamine and sulphadiazine verus pyrimethamine and clindamycin showed that the latter is an acceptable alternative if pm-sdz was not tolerated[43]. However, life long prophylaxis is necessary to prevent relapses. Studies to examine the efficacious effect of cross prophylaxis with tmp-smz is underway.

Other common protozoa include *Cryptosporidium* which is one of the most devastating and unpleasant opportunistic infection that occurs in AIDS[44]. Paramomycin, a non-absorbable aminoglycoside had been tried with small amounts of success[45] and octreotide (a somatostatin analogue) has offered good symptomatic relief[46]. Spiramycin and interleukin-2 have been tried with little success[32]. Isopora is another common invader and has been treated with co-trimoxazole and fansidar with some success[44]. Microsporidia is yet another troublesome infection and is more often encountered than cryptosporidia. Albendazole treatment has proven to be useful in such cases[47].

**Fungi**

*Candida albicans* is probably the commonest opportunistic organism in HIV infected patients. The spectrum of disease can range from mild mucosal disease to infrequent severe fulminant septicaemia. Initial treatment with topical agents in mild cases with nystatin, amphotericin, clotrimazole or miconazole will ameliorate symptoms but oral agents like ketoconazole, fluconazole and itraconazole are usually required[48]. As relapse always occur and maintenance therapy is usually required, drug interaction especially with ketoconazole poses significant disadvantage. Drug hypersensitivity is infrequent although in rare situations patients are intolerant to all drugs except amphotericin. Currently, fluconazole and itraconazole are favoured as they are also effective against *Cryptoccocus neoformans*[32].

*Cryptococcus neoformans* has been reported in 5% of patients with AIDS and the mortality is high when treatment is delayed[49]. Fluconazole is as effective an agent as amphotericin B (0.5-1 mg/kg/day) for acute cryptococcal meningitis when there is no alteration of mental state[50]. Currently, new trials with Liposomal-Amphotericin B ( between 1 mg-3 mg/day) are being conducted, preliminary reports showed encouraging signs with fewer side effects. Frequent relapse is common and maintenance therapy either with amphotericin B or fluconazole (200 mg/day) is life long[51]. Frequent and persistent vaginal Candidiosis is seen in many seropositive females and it is recommended that they be treated with fluconazole 50 mg/day.

**Viruses**

Cytomegalovirus (CMV) in HIV individuals frequently causes pulmonary disease in conjunction with *pneumocystis* pneumonia. CMV chorioretinites, enterocolites and possibly pneumonia is being treated with ganciclovir (5 mg/kg/BID), although therapy is necessary for an indefinite period because of high frequency of relapse[51]. Intravenous forscanet (120 to 180 mg/kg/day) is noted to be superior to intravenous ganciclovir in survival benefits[52]. There have been cases of ganciclovir resistance noted and current trials with forscanet and ganciclovir combination are in progress. Intravitreal ganciclovir is now gaining popularity with many centres[53]. Mucocutaneous herpes simplex infections are common in AIDS patients and usually respond to acyclovir and require suppressive therapy because of recurrent disease. Herpes zoster responds similarly although in severe cases intravenous infusion may be necessary. Some virus like *papovavirus* which causes progressive multifocal leucoencephalopathy (PML) in HIV patients has no known effective therapy[54].

**Bacteriae**

Standard triple or quadruple therapy consisting of rifampicin, ethambutol, isoniazide with pyrazinamide appears to be satisfactory treatment for mycobacterium tuberculosis regardless of site[55] for at least nine months. Possibility of relapse after some months does occur[56] and therefore close follow-up is necessary. Regardless of age, HIV infected patients with a positive PPD test but no clinical evidence of infection should receive isoniazide pophylaxis when it is not contraindicated by other medical conditions[57]. Unfortunately, much less success has been achieved with treatment of atypical myobacterium and currently available regimes are unsatisfactory and require to be given for life[58]. The treatment of Mycobacterium Avium Intracellulare Complex (MAC) has been plagued with resistant strains[59], azithromycin[60] (500 mg TID) havebeen shown to decrease fevers, blood culture quantitatively and night sweats.

Currently, combination drug therapy is the mode of treatment and it involves rifampicin, clofazamine, ethambutol, amikicin, clarithromycin and azithromycin. Rifabutin (Mycobutin)$^{R}$ has recently been advocated as a drug of primary prophylaxis[61] for MAC. *Salmonella enterites* and bacteremia can cause severe generalised illness and have been reported[7]. But early relapse is frequent and like most other infections, maintenance therapy is required. The drug of choice appears to be trimethoprim[7].

Capsulated bacterial infection by *pneumoccocus, haemophilus, bramanhella* may be the result of the immunoglobulin G2 subclass deficiency[62]. Bacterial infections secondary to neutropenia can result in overwhelming infection with *pseudomonas* and *staphylococcus*. Fortunately this happens infrequently and is surprisingly well tolerated[63].

**Other Infections**

Many other infectious processes take advantage of the immunosuppresion in HIV patients which have not been mentioned above. For example, the treatment of syphilis (penicillin in all stages; doxycycline and erythromycin to be avoided) with present schedules may be inadequate[64]. Coinfection with HTLV-1 is common in certain drug using populations and may result in severe ulcerative skin lesions[65]. It is hoped that with more widespread use of antivirals the prevalence and severity of these infections would decrease and in fact this has been the preliminary experience[9].

## MALIGNANCIES

**Kaposi's sarcoma**

The rational therapy of Kaposi's sarcoma associated with HIV infection is obscured by the lack of adequate knowledge of the natural history of the disease and the presence of lesions in a setting of variable severe immune dèficiency[66]. In addition, treatment of lesions by cytotoxic agents aggravate the pre-existing immunodeficiency. An assessment of any treatment should bear this in mind. Hence, some treatment regimes recommend zidovudine and interferon in combination[67,68]. A summary of the drugs used and their present status is presented in Table II. Since only some 25% of patients die directly from Kaposi's sarcoma[69], treatment should generally be aggressive only in advanced cutaneous or pulmonary Kaposi's[70] sarcoma. More recently, Liposomal - daunorubicin (Daunoxome$^{R}$) (400 mg/m$^{2}$ per 2 weeks) intravenous therapy for advance Kaposi's sarcoma have yielded encouraging results with minimal side-effects[70]. Besides chemotherapy, it is useful to remember that

Kaposi's sarcoma is radiation responsive although the radiation is palliative[71] rather than curative.

**Table II – Drugs used in 1993 to treat Kaposi's Sarcoma occurring in HIV infected patients**

| Agent | Response and Status |
|---|---|
| Etoposide (VP-16-213) | 75% partial response |
| Vinblastine | 25% partial response |
| Adriamycin, Bleomycin, Methotrexate | Awaiting clinical trials |
| Interferon-alpha | 50% response |
| Thymic hormones | Inactive |
| Isoprinosine | Inactive |
| Cimetidine | Experimental |
| Interleukin 2 | Experimental |
| Liposome-Daunorubicin | Phase II trials |

### Lymphomas and other neoplasms

Non-Hodgkins lymphoma is increased in frequency especially in extra nodal sites and is probably attributable to the complex result of EBV infection, HIV antigenic stimulation and T cell dependent HIV activation[72]. Patients with AIDS associated non-Hodgkin's lymphoma do poorly due to diminished primary response to chemotherapy, high relapse rates and complicating infections[73]. The drug combinations that have been used include cyclophosphamide, vincristine, cytosar, etoposide and methotrexate[62] and central nervous system intrathecal prophylaxis using cytosine arabinoside[74].

Hodgkin's lymphoma, when it does occur, has a poor prognosis[75]. There is a higher incidence of many epithelial neoplasias which have a virus-cancer association, for example the cloacogenic carcinoma of the anus associated with papilloma virus[76].

Female HIV positives are now recognised to have more extensive cervical dysplasia with rapid progression to invasive neoplasia. In view of this it is recommended that annual cervical cytology be done and since January 1993, invasive cervical dysplasia is considered an AIDS defining condition[77].

Many of these tumours are treated in the usual way with judicious surgery and appropriate chemotherapy. Steroids are not totally contraindicated and have been beneficial in immune mediated thrombocytopenia occurring in HIV infected individuals[78].

## CONCLUSION

The role of drugs in the management of HIV infected individuals ranges from treatment of simple infections to life threatening infections and malignancies. This review has omitted most of the infections and malignancies not specifically associated with HIV infection. However they should be considered and treated in the standard manner. The main problem in pharmacological therapy of this immunodeficiency state is the constant requirement for prophylaxis or continuous suppressive therapy as complete cure is normally remote.

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