Antifungal Use for Opportunistic Infection in HIV Patients: Comparison of Efficacy and Safety

Corresponding Author:
Ms. Sabariah N Harun,
Lecturer, School of Pharmaceutical Sciences, Universiti Sains Malaysia - Malaysia

Submitting Author:
Ms. Mei H E,
Undergraduate student, School of Pharmaceutical Sciences, Universiti Sains Malaysia - Malaysia

Article ID: WMC002674
Article Type: Review articles
Submitted on: 18-Dec-2011, 09:21:17 AM GMT   Published on: 19-Dec-2011, 03:45:21 PM GMT
Article URL: http://www.webmedcentral.com/article_view/2674
Subject Categories: AIDS
Keywords: HIV, Opportunistic fungal infection, Comparison, Efficacy, Safety


Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Antifungal Use for Opportunistic Infection in HIV Patients: Comparison of Efficacy and Safety


Abstract

Background: Fungal infections always occur in HIV patients due to depressed immunity. The most common fungal infections are candidiasis, cryptococcal meningitis and histoplasmosis.

Objectives: To compare the efficacy and safety of the antifungal available for the three most common opportunistic fungal infections in HIV patients.


Results: Based on our review, candidiasis can be sub-divided into localized (oropharyngeal and vulvovaginal) and systemic candidiasis. Fluconazole is found to be the most common used due to its high efficacy treating candidiasis. Prophylaxis of cryptococcal meningitis can be done by administering ketoconazole or itraconazole depending on whether it is primary or secondary prophylaxis. Treatment using flucytosine in combination with amphotericin B has additive effect and appears to be the most effective regimen for cryptococcal meningitis therapy. Histoplasmosis is characterized by pulmonary and disseminated histoplasmosis and the mainstrays of therapy for histoplasmosis are amphotericin B and itraconazole. The most prominent side effects of amphotericin B include nephrotoxicity, acute toxicity and hypokalemia. Flucytosine and itraconazole induces gastrointestinal side effects and bone marrow depression while hepatotoxicity is found to be the major side effect of flucytosine and ketoconazole. Ultimate care must be taken when administering ketoconazole as it has considerable drug interactions with other medications. In patients treated with fluconazole, the most common adverse effects include phlebitis, headache and nausea, abdominal pain, diarrhoea and rashes.

Conclusions: From our review, it appears to have different drug of choice of antifungals for different opportunistic fungal infections. Besides, it is found that different efficacy of different drugs form the basis guideline for the therapeutic regimen in treating opportunistic fungal infections. However, therapeutic regimens recommended also induce various types of adverse reactions or side effects. Therefore, dose adjustment and therapeutic drug monitoring must be performed accordingly and routinely to avoid unnecessary complications.

Key words: HIV, opportunistic fungal infection, comparison, efficacy, safety.

Introduction

In Malaysia, the first HIV infection case was reported in the year 1986 (Wang & Ismail, 1999). HIV pandemic has been on the rise from 200 cases in year 1990 to 5107 cases in the year 2000 (Nissaptorn, et al., 2004). HIV patients are always associated with opportunistic infections due to severely suppressed immunity. These opportunistic infections are caused by virus, bacteria, parasites, and fungal. Fungal infections are common in tropical country like Malaysia. Among the most common fungal infections are candidiasis which is normally caused by Candida albicans, cryptococcal meningitis which is caused by Cryptococcus neoformans and histoplasmosis which is caused by Histoplasma capsulatum.

Efficacy of a drug is the capability of a drug to produce a positive effect. It is important to identify the site of infection before a drug therapy can be administered. Each drug and different dosage forms lead to differences in efficacy on the particular disease. The efficacy of the drug must be taken into consideration so that the drug therapy is effective.

Safety of a drug covers the aspects drug-drug interaction and side effects of the drugs. Most of the antifungal has adverse effects to certain extent. The patient’s medical condition must be monitored before administering the drugs. Besides, health professionals must be aware of the other drug therapy that the HIV patients are undergoing. This is due to susceptibility of the patients towards other opportunistic infections. Our objectives are to compare the efficacy and safety of the antifungal available for the three most common opportunistic fungal infections in HIV patients.

Candidiasis

The clinical manifestations of Candida infections can
be from mucocutaneous to life-threatening invasive candidiasis (Zawadka & Marczynska, 2010). Common types of opportunistic infections caused by candida species among the HIV patient in Malaysia can divided into two main types, namely the localized candidiasis and the systemic candidiasis. The most common localized candidiasis is the oropharyngeal and vulvovaginal candidiasis. The systemic candidiasis is oesophagitis candidiasis (Kaplan, et al., 2009).

The clinical manifestation of oropharyngeal candidiasis is painless, creamy whitish plaque-like lesions of the buccal or oropharyngeal mucosa or tongue surface. Vulvovaginal candidiasis is characterized by the burning and itching sensations of the vagina. It can also characterized by the curdy and thick vaginal discharge. Oesophageal candidiasis results in retrosternal burning pain or discomfort and adynophagia (Kaplan, et al., 2009).

i. Localized Candidiasis
a. Oropharyngeal candidiasis (OPC)
Early stage and uncomplicated oropharyngeal candidiasis can be treated with topical clotrimazole troches or oral polyenes such as nystatin or amphotericin B suspension (Rex, et al., 2000). In infants, troches should not be given because resistance to clotrimazole can be developed easily if they are exposed to azole drugs. The developed resistance is related to refractory mucosal candidiasis (Pelletier, et al., 2000). For initial treatment of OPC, systemic therapy with oral azoles such as fluconazole, ketoconazole or itraconazole is also effective (Pons, Greenspan & Debruin, 1993; Pons, et al., 1997). Fluconazole is more effective than nystatin suspension for initial treatment. Oral fluconazole is more suitable for children than topical treatment (Pons, Greenspan & Debruin, 1993; Goins, et al., 2002).

Itraconazole oral solution and fluconazole have similar efficacy for one to two weeks but the former is less well tolerated than the latter (Phillips, et al., 1998; Vazquez, et al., 2006). Itraconazole should be taken in the absence of food because gastric acid will enhance absorption of itraconazole. There are two dosage forms of itraconazole: capsules and oral solution. These two should not be used interchangeably because at the same dose, oral solution has less exposure than that of capsules and absorption of capsule formulation varies (Mofenson, et al., 2009).

In adult, oral fluconazole is effective for topical therapy for oropharyngeal candidiasis. It is because it is better to be tolerated and more convenient usage. Thus, oral fluconazole becomes the drug of choice for oropharyngeal candidiasis (Pappas, et al., 2004). Same as infant, initial treatment for adults can be treated by topical therapy such as clotrimazole troches, nystatin suspension or pastilles, or once-daily miconazole mucoadhesive tablets (Van, et al., 2004).

Posaconazole oral solution has similar effectiveness as fluconazole and is generally better tolerated than itraconazole. Posaconazole is proven more effective than fluconazole to sustain clinical success after the anti-fungal therapy is discontinued (Vazquez, et al., 2006).

Topical non-absorbed therapy using the ‘swish and swallow’ principle is usually effective and is used in patients with single occurrence of oropharyngeal candidiasis as first-line therapy for 10-14 days. Local therapy consists of amphotericin B suspension or tablets, nystatin lozenges or clotrimazole troches. A study found that clotrimazole troches are as effective as itraconazole oral solution (Linpiyawan, Jitteprasert & Sivayathorn, 2000). A comparative study of itraconazole oral capsules (200mg once daily) and clotrimazole troches (10mg five times daily) have same therapy effect. Itraconazole has faster response and clotrimazole has faster relapse rate (Blathford, et al., 1990). However, fluconazole capsules are more effective than nystatin and at least equivalent to clotrimazole for thrush therapy (Pons, Greenspan & Debruin, 1993; Pons, et al., 1997).

b. Vulvovaginal Candidiasis
Vulvovaginal candidiasis occurs in HIV-infected women and is usually uncomplicated (90%) and responds to rapid oral or topical therapy including oral fluconazole, topical azoles (clotrimazole, butaconazole, miconazole, ticonazole or terconazole) and itraconazole oral solution. Severe or recurrent of vaginitis needs the treatment of oral fluconazole or topical antifungal therapy for at least one week (Kaplan, et al., 2009).

Imidazole treatment is effective against C. glabrata infections (Sobel, 1985). Strains resistant to ketoconazole or fluconazole have been described (Warnock, 1988), causing refractory cases. On the other hand, fluconazole is specific for C. albicans than other imidazoles (Liss & Letourneau, 1989).

ii. Systemic disease of oesophagus
a. Candida oesophagitis
There is one prospective trial comparing two oral agents: fluconazole (100-200mg qid) and ketoconazole (200-400 mg qid) in 169 patients. Result shows fluconazole has higher rates of endoscopic (91% vs. 52%) and clinical (85% vs. 65%) cure than that of ketoconazoles (Lame, et al., 1992). Since AIDS patients have decrease gastric acid secretion, (Dieterich & Rahmin, 1991) the difference of efficacy is because of ketoconazole requires acid for absorption but not for fluconazole (Blum, et al., 1991).
Amphotericin B is effective at relatively low doses in Candida esophagitis (0.3 mg/kg/day for a total dose of less or equal to 500 mg (Parente, et al., 1991). An addition of new azoles such as voriconazole and posaconazole and also a new class of drug, the echinocandins (caspofungin, micafungin and anidulafungin) have provided more drug of choice to treat opportunistic fungal infection (Kofla & Ruhnke, 2005; Nagappan & Deresinski, 2007; Metcalf & Dockrell, 2007). There are limited studies that report the usage of agents in oesophageal candidiasis and their efficacy in other settings (condition) in HIV patient (Ally, et al., 2001; Vazquez, et al., 2006; Villanueva, et al., 2002; Krause, et al., 2004; de Wet, et al., 2004).

Echinocandins have limited drug interactions and adverse effect, and therefore is used in severely ill patients. They are also good drug choices for hepatic and renal dysfunction patients. According to HIV-specific data, usage of echinocandin is limited to HIV-seropositive individuals (Metcalf & Dockrell, 2007).

Systematic antifungals are used to treat oesophageal candidiasis effectively (Migliorati, et al., 2004). Fluconazole given orally or intravenously or oral itraconazole solutions, administered for 2 to 3 weeks, are highly effective for treatment of Candida esophagitis (Wilcox, et al., 1997). Voriconazole or caspofungin are also effective in treating esophageal candidiasis in HIV-infected adults. They must be administered intravenously due to limited bioavailability (Mora-Duarte, et al., 2002; Walsh, 2002; Deresinski & Stevens, 2003).

Although IV caspofungin or IV voriconazole are effective in treating esophageal candidiasis among HIV-infected patients, instead oral or IV fluconazole remains the preferable therapies (Migliorati, et al., 2004). Two additional parenteral echinocandins (micafungin and anidulafungin) are also approved to treat esophageal candidiasis. Although the three echinocandins have similar efficacy as fluconazole, they all have a greater relapse rate compared with fluconazole (de Wet, et al., 2004; Krause, et al., 2004).

Crypococcal Meningitis

Cryptococcal meningitis is the infection of the meninges of the brain which is caused by encapsulated yeast Cryptococcus neoformans (Casadevall & Perfect, 1998) that is widely distributed and can be found in typical soil (Dugdale & Vyas, 2010). Cryptococcal meningitis is a common opportunistic in immuno-compromised patients such as Acquired Immunodeficiency Syndrome (AIDS) patients in Africa and also Southeast Asia (Holmes, et al., 2003; Chariyalertsak, et al., 2001a). It often affects patients with weak immune system such as patients with diabetes, lymphoma and AIDS (Dugdale, et al., 2010). Commonly, cryptococcal meningitis is often associated with Human Immunodeficiency Virus (HIV) patients whereby their T-helper CD4 counts is less than 100 cells/µL (Bicanic & Harrison, 2004). Upon clinical presentation for acute onset (less than 7 days) and chronic onset (more than 30 days), patients usually present with fever, malaise, headache, having altered mental status and nuchal pain suggesting meningeal irritation (Bicanic & Harrison, 2004; Subramanian & Mathai, 2005). Basically, primary prophylaxis is not necessary for cryptococcal meningitis since antifungal prophylaxis is not to be used routinely to prevent cryptococcosis due to rarity of the disease, lack of survival benefit, possibility of drug interaction and potential development of antifungal drug resistance. Nevertheless, life-long secondary prophylaxis after completion of the initial treatment regimen is indicated (Powderly, et al., 1996) and recommended for patients who have completed initial therapy for cryptococcal infection (French, et al., n.d.).

i. Treatment

a. Amphotericin B

In 1950s, treatment using Amphotericin B (a polyene) was known to be the first effective therapy for non-HIV-associated infection. However amphotericin B is a concentration-dependent drug (Dodds, Drew & Perfect, 2000) whereby studies on 0.7 mg/kg/day Amphotericin B regimen produces greater improvement outcome compared to 0.3-0.5 mg/kg/day in 10 weeks of therapy (Van Der Horst, et al., 1997). Recommended dose for amphotericin B is 0.7-1.0 mg/kg/day and it is administered through intravenous infusion. Further studies showed that the administration of high dose amphotericin B at 1 mg/kg/day with or without fluucytosine for 2 weeks follow by consolidation therapy using itraconazole or fluconazole had produced a positive outcome whereby 94% (29 out of 31) patients survive cryptococcal infection with zero mortality rates (DeLalla, et al., 1995). Liposomal amphotericin B acts as an alternative lipid formulation, delivering of larger doses of amphotericin B simultaneously giving same effectiveness while less nephrotoxicity comparing to conventional amphotericin B. From a randomized study, the rate of culture of conversion of the Cerebrospinal Fluid (CSF) was higher when administrating liposomal amphotericin B at 4 mg/kg/day rather than the conventional amphotericin B.
Leenders & Reiss, 1997).

b. Flucytosine

Flucytosine is often prescribed along with amphotericin B but not alone due to the development of resistance in mono-therapy of flucytosine (Bicanic & Harrison, 2004). It is proven that the combination of amphotericin B (0.7 mg/kg/day) with flucytosine (150 mg/kg/day) will lead to an additive effect (Bicanic & Harrison, 2004; Medoff, Comfort & Kobayashi, n.d.; Block & Bennet, n.d.) as shown in clinical trials and also pre-clinical studies in both HIV and non-HIV associated infection patients and eventually resulting a successful treatment (Bicanic & Harrison, 2004; Larsen, Leal & Chan, 1990). However, there is another studies conducted whereby the combination of amphotericin B with flucytosine (up to 75-100 mg/kg/day) did not change the survival of patients with Acquired Immunodeficiency Syndrome (AIDS) and cryptococcal disease compared to mono-therapy using amphotericin B (Menichetti, Fiorio & Tosti, 1996). Therefore, combination of amphotericin B with flucytosine and amphotericin B alone has been utilized whereby the findings appear to be an exponential decrease in CSF cryptococcal colony-forming units (CFUs) (Brouwer, et al., 2004).

c. Fluconazole

Regarding the efficacy of fluconazole, comparative clinical trial shows that not much significant decrease in term of the efficacy when treatment is conducted using amphotericin B at 0.4-0.5 mg/kg/day and fluconazole at 200 mg/day, a lower dose compared to current recommended dose (400 mg/day), yielding a result for negative culture of the CSF by 40% vs 34% and 14% vs 18% of rate of mortality for 10 weeks (Saag, et al., 1992). Comparing amphotericin B with fluconazole, clinical study shows that amphotericin B has a shorter median time for the CSF sterilization, which are 42 instead of 64 days (Saag, et al., 1992). Fluconazole also plays an important role in consolidation therapy phase. Clinical study reviewed that a 2 weeks of induction therapy phase using amphotericin B at 0.7 mg/kg/day, with or without flucytosine at 100 mg/kg/day follow by consolidation phase using fluconazole or itraconazole at 400 mg/day for 6-8 weeks forms a good regimen combination whereby having the rapid initial action of amphotericin B and a prolonged therapy using an azole that can prevent toxicity of amphotericin B in a long term therapy.

Itraconazole serves as an alternative oral agent. However, the CSF sterilization in 10 weeks during consolidation phase is found to be less effective than fluconazole, same outcome goes to another study regarding the maintenance therapy (Bicanic & Harrison, 2004). Clinical study also showed fluconazole was 15% more effective than itraconazole in terms of CSF sterilization (Levitz, et al., 1999). A further study comparing efficacy using lower dose of fluconazole with itraconazole at 200 mg/day respectively is conducted whereby the outcome appears to be proving fluconazole is superior in maintenance therapy of cryptococcal infection (Bicanic & Harrison, 2004; Van Der Horst, et al., 1997).

ii. Prophylaxis

a. Primary

Primary prophylaxis with azole antifungals has been observed to be effective in lowering the incidence rate of cryptococcal meningitis in those with advanced HIV infection (Charityalertsak et al., 2001b; Powderly, 1995; Mckinsey, Wheat & Cloud, 1999). However, primary prophylaxis for cryptococcal meningitis is not recommended in developed countries due to the lack of evidence of any survival benefit, the cost and the risk of promoting fungal resistance (Masur, Kaplan & Holmes, 2002).

It is concluded by studies that ketoconazole can be used as primary prophylactic agent against Cryptococcal meningitis and it was effective. The application of this agent may be very useful to developing countries, because of the price issue where it is cheaper than other amidazoles, ultraconazole and fluconazole, and much easier to take as compared to amphotericin B (Sprinz & Matias, 1992).

b. Secondary

Secondary prophylaxis with fluconazole and itraconazole are effective at preventing cryptococcal meningitis in HIV-positive adults (Moosa & Coovadia, n.d.; Kaplan et al., n.d.; Lopez et al., n.d.; El-Sadr et al., n.d.; Chariyalertsak et al., 2001b) but are only associated with a survival benefit in patients with either very low CD4 counts.

Contrasting between itraconazole and fluconazole, secondary prophylaxis with itraconazole is less effective in reducing relapses of successfully treated cryptococcal meningitis over 12 months in people with HIV infection (BMJ publishing group, 2008). Simultaneously, another study in Thailand has also indicated that itraconazole prophylaxis at 200 mg/day significantly reduced the risk of invasive fungal infections in those with advanced HIV disease (CD4 counts less than 100 cells/ml) but did not result in improved survival (Subramanian & Mathai, 2005).
**Histoplasmosis**

Histoplasmosis is an illness of infection resulting from infection with the fungus which is Histoplasma capsulatum. This infection can produce a spectrum of illness, from subclinical infection to progressive disseminated disease. Opportunistic histoplasmosis develops as chronic pulmonary histoplasmosis in those with a structural defect in the lung or as disseminated (progressive or spread) histoplasmosis in patients with cellular immune deficiency (due to immunosuppressants or HIV infection). In disseminated disease, the infection can spread from lung to other organ via bloodstream. Untreated, this latter form of infection may be rapidly fatal (Bradsher, 1996).

**i. Pulmonary histoplasmosis**

Chronic cavitary disease can result in significant loss of lung function especially in patients with underlying structural lung disease. In cases of acute disease with only mild to moderate symptoms, treatment is not recommended because more than 95% of patients improve without therapy within 3 weeks. If symptoms do not improve after 1 month, a 6 to 12 weeks course of itraconazole is recommended. A lipid formulation of Amphotericin B is preferred and should be given for the initial 1 to 2 weeks of treatment, followed by itraconazole to complete a 3 month course of therapy. If patients have acute respiratory distress symptoms, Methylprednisolone is indicated for the first 1 to 2 weeks of therapy. This treatment is usually effective, although relapse occurs in up to 15% of patients. As a result of histoplasmosis complication, mediastinal granuloma is developed. Itraconazole therapy is reasonable for symptomatic patients, and surgery is an option for patients who do not respond to pharmacological treatment. Pulmonary nodules (histoplasmomas) occur at sites that are previously affected by Histoplasma and normally enlarge or cavitate slowly. If patients have multiple nodules, acute pulmonary histoplasmosis is suspected and must be treated. If hemodynamic compromise occurs, effusion drainage will be required. Antifungal agents are needed when corticosteroids are used whereby itraconazole should be given.

Finally, arthritis and arthralgias may be resulted from an inflammatory complication of acute pulmonary histoplasmosis. Erythema nodosum can occur as well. NSAIDs help in recovery, although corticosteroids may be required in the setting of severe disease, whereby itraconazole should be given as well (Duane, 2009).

**ii. Disseminated Histoplasmosis**

Patients with symptomatic disseminated histoplasmosis are able to recover from the infection without antifungal therapy in some extent, but this is abnormal. Generally, all patients with disseminated histoplasmosis should be treated with an antifungal agent. Patients who are not severely ill can be treated with oral itraconazole of 200 mg twice daily.

Fluconazole is less effective than itraconazole and is considered to be a second-line agent. The dosage of fluconazole is 400 to 800 mg daily when it is used. In AIDS patients, the dosage should be 800 mg daily because of a failure rate of 50% in a cohort who had mild to moderately severe disseminated histoplasmosis and who was treated with 600 mg daily. Patients with severe disseminated infection should be treated initially with amphotericin B at a dosage of 0.7 to 1 mg/kg daily or a lipid formulation of amphotericin B at a dosage of 3 to 5 mg/kg daily. Lipid formulations of amphotericin B are used in most patients because of their reduced toxicity (Kaufman, 2007).

**iii. Treatment**

Amphotericin B in the form of intravenous infusion is effective in histoplasmosis and because of its low toxicity and should be expected to be effective in human histoplasmosis and it is proven to be the first effective treatment for histoplasmosis (Baum, Schwarz & Wang, 1957).

Itraconazole has been effective in primary as well as chronic suppressive treatment of histoplasmosis in patients with AIDS. In addition, in the treatment of non-AIDS-associated progressive disseminated histoplasmosis, itraconazole has been shown to be effective in cases of chronic pulmonary histoplasmosis, although a relatively high relapse rate can be expected, similar rates of relapse have been associated with amphotericin B therapy as well (Bradsher, 1996). However, some patients are unable to tolerate itraconazole or are at risk for significant drug interactions. Therefore, alternative forms of therapy are required (McKinsey et al., 1996).

Fluconazole is a broad-spectrum triazole antifungal drug that possesses in vitro activity against Histoplasma capsulatum and has been effective in both immunocompetent and immunosuppressed murine models of histoplasmosis. Fluconazole has been modestly effective as induction therapy and maintenance therapy for disseminated histoplasmosis in patients with AIDS, and non-HIV-infected patients have also been treated successfully. Fluconazole remains a second-line agent for the treatment of histoplasmosis (McKinsey et al., 1996).

Ketoconazole is less toxic compare to amphotericin B. In cases of chronic pulmonary histoplasmosis,
ketoconazole have been shown to be effective, although a relatively high relapse rate can be expected similar rates of relapse have been associated with amphotericin B therapy as well (Bradsher, 1996).

In summary, fluconazole therapy was only moderately effective for treatment of chronic pulmonary histoplasmosis and disseminated histoplasmosis at the doses studied, but it was highly effective in the two patients who had progressive acute pulmonary histoplasmosis. The previously reported efficacy of itraconazole therapy for histoplasmosis in non-HIV-infected patients is superior to the efficacy of fluconazole observed. The use of fluconazole for treating histoplasmosis in non-HIV-infected patients is to be reserved for mild to moderate disease in the following patients those who cannot take itraconazole because of its toxicity, those with impaired absorption due to achlorhydria, or those receiving drugs that may potentially interact with itraconazole. Multiple antifungal agents are available for histoplasmosis, but amphotericin B and itraconazole are the mainstays of therapy.

**Comparison of Safety**

### i. Amphotericin B

**Acute toxicity**

Amphotericin B had more side effects of acute infusion-related reactions includes nausea, vomiting, rigors, fever, hypertension or hypotension and hypoxia than those receiving other antifungal drugs. These side effects were observed most frequently at the time of the first infusion and disappeared during subsequent infusions. These clinical side effects of amphotericin B have been partially explained by the release of interleukin-1, prostaglandin E-2, and tumor necrosis factor in response to amphotericin B administration (Pathak, et al., 1998).

**Nephrotoxicity**

Amphotericin B nephrotoxicity is caused by enhanced tubuloglomerular feedback. Tubuloglomerular feedback is a normal intrarenal mechanism whereby increased solute delivery to the distal tubule results in afferent arteriolar vasoconstriction. Amphotericin B, possibly because of its effects on biologic membranes, increases monovalent ion delivery to the distal tubule, causing afferent arteriolar vasoconstriction, most likely due to local adenosine release (Anderson, 1995).

**Hypokalemia**

In patients receiving amphotericin B, there also was a greater frequency of moderate hypokalemia and severe hypokalemia. Hypokalemia occurred more often with higher amphotericin B doses.

**How to overcome?**

Since the vasoconstrictive effects of amphotericin B are clearly calcium dependent, it makes sense to hypothesize that calcium channel antagonists might reduce amphotericin B nephrotoxicity.

### ii. Flucytosine

**Gastrointestinal Side Effects**

Side effects reported while taking flucytosine include diarrhea, nausea, vomiting and diffuse abdominal pain (Benson & Nahata, 1988). Besides that, liver enzymes also marked an increased in level but normally can be overcome by reducing the dose of flucytosine. In addition, increase in concentration of bilirubin in serum also noted in patient taking flucytosine but can be reversed by terminating administration of flucytosine (Scholer, 1980).

**Bone Marrow Depression**

Bone-marrow depression rises to be the most severe toxicity caused by flucytosine. Several severe and life-threatening pancytopenias have been reported associated with intake of flucytosine (Kauffman & Frame, 1977; Schlegel et al., 1970; Meyer & Axelrod, 1974).

**Hepatotoxicity**

Flucytosine is concentration-dependent drug. Cases such as swelling of liver has been reported rarely (Scholer, 1980). However, hepatotoxicity is avoidable by maintaining peak concentration of flucytosine below 100 mg/L and is reversible by reducing the dose or termination of therapy using flucytosine (Francis & Walsh, 1992; Stamm et al., 1987).

**How to overcome?**

Adverse reactions and side effects of flucytosine can be overcome by monitoring the serum drug concentrations. For patients with renal failure or taking nephrotoxic drugs, or having gastrointestinal or haematological toxicity, therapeutic drug monitoring (TDM) and dosage adjustment is vital (Benson & Nahata, 1988).

### iii. Fluconazole

**Clinical adverse effect**

The clinical adverse effects of fluconazole are phlebitis, headache and nausea, abdominal pain, diarrhoea and rash. According to the study, the most common clinical adverse effect is phlebitis. The only severe drug-related adverse event was cellulitis causing fluconazole infusion is more difficult to be administered to the patient (Villaneuva, A. et al. 2002).

**Skin problem**

Skin rashes can occur and severe skin condition like Steven Johnson’s syndrome and exfoliative disorder are reported.
Laboratory adverse effects
The laboratory adverse effects are decreased white blood counts, hemoglobin levels, and serum albumin concentrations (Villaneuva, A. et al. 2002).

Hepatobiliary adverse effects
There is temporary elevation of liver enzymes and the severity varies among patients. The worst condition is that it may lead to fatality due to liver failure. There are also increase of serum levels of enzymes like alkaline phosphatase and aminotransferase (Villaneuva, A. et al. 2002).

How to overcome?
Administer fluconazole orally often produces gastric irritation, heartburn and vomiting, ulceration development and causes patients are less compliance with long term therapy. To minimize these side effects, topical admininisation of fluconazole in cutina lipogel and gel microemulsion has been studied (El-laithy & El-Shaboury, 2002). The application of emulsions as topical drug carrier systems for the percutaneous absorption of fluconazole has been investigated (Ayub, et al., 2007).

iv.Itraconazole
Hepatotoxicity
Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing should be performed.

Gastrointestinal
Common adverse effects of itraconazole therapy include gastrointestinal effects diarrhoea, skin rash, and reversible increases in hepatic enzymes. Less common but more severe side effects such as congestive heart failure and idiosyncratic hepatic failure have been reported.

How to overcome?
In general, use of itraconazole should be avoided with severe liver disease patients. However, if itraconazole is used, concurrent monitoring of itraconazole levels along with hepatic enzymes and bilirubin may be prudent given that liver disease is associated with multiple factors such as protein binding, drug distribution that can affect drug distribution and clearance (Lewis and Prince, 2001).

v.Ketoconazole
Hepatotoxicity
33 out of 54 cases in an US study show ketoconazole-induced hepatitis whereby women of age more than 40years old are more likely to be affected. 27 people in that study had jaundice. One-third of ketoconazole-induced hepatitis cases are accompanied by anorexia, malaise, vomiting and nausea (Lewis, et al., 1984).

Toxicity due to low albumin level
Since ketoconazole is highly plasma protein bound (83.7%), it should be used with caution for the patients who are malnutrition (Daneshmend & Warnock, 1988). Patients who are malnutrition will not have sufficient protein to distribute the drug and this will results in toxicity of the free, unbound drug in the body.

Steroid synthesis blocker
Ketoconazole blocks the cortisol response to adrenocorticotropic hormone significantly 4 hours after 400mg/600mg dose. This inhibition lasts for 8 to 16 hours. These findings showed that ketoconazole reduces the adrenal androgen response. Ketoconazole must be used with caution when it is used in high or multiple dose as it is a powerful steroid synthesis blocker (Pont, et al., 1982).

Drug-drug interaction
Ketoconazole has significance drug interactions with warfarin, chlordiazepoxide, methylpredisolone, cyclosporine and microsomal enzymes inducing drugs (Daneshmend & Warnock, 1988).

How to overcome?
In order to overcome all these problems, dose adjustment must be made and drug monitoring must be done accordingly.

Conclusion
HIV patients are often associated with opportunistic infections due to their weakened body immunity system. In this case, we focused on three fungal infections such as candidiasis, cryptococcal meningitis and histoplasmosis which appear to be the most common opportunistic infections in HIV patients. From our study, common antifungals used are amphotericin B, flucytosine, fluconazole itraconazole and ketoconazole and it appears to have different drug of choice of antifungals for different opportunistic fungal infections in HIV patients. Besides, it is found that different efficacy of different drugs form the basis guideline for the therapeutic regimen in treating opportunistic fungal infections.

However, those therapeutic regimens recommended also induce various types of adverse reactions or side effects such as nephrotoxicity, gastrointestinal side effects and hepatotoxicity. Therefore, dose adjustment and therapeutic drug monitoring must be performed accordingly and routinely to avoid unnecessary complications.
Acknowledgment

No sources of funding are used to assist in preparing this article. All authors have accessed to the articles through University Sains Malaysia. The authors are grateful to Dr Amin Malik Shah Abdul Majid for giving us this opportunity to produce this review article.

References

development of cutina lipogels and gel microemulsion for topical administration of fluconazole. AAPS Pharm SciTech., 34, 1-9.
manifestations and management of cryptococcal infection. Journal of Postgraduate Medicine, 51(5).
Disclaimer

This article has been downloaded from WebmedCentral. With our unique author driven post publication peer review, contents posted on this web portal do not undergo any prepublication peer or editorial review. It is completely the responsibility of the authors to ensure not only scientific and ethical standards of the manuscript but also its grammatical accuracy. Authors must ensure that they obtain all the necessary permissions before submitting any information that requires obtaining a consent or approval from a third party. Authors should also ensure not to submit any information which they do not have the copyright of or of which they have transferred the copyrights to a third party.

Contents on WebmedCentral are purely for biomedical researchers and scientists. They are not meant to cater to the needs of an individual patient. The web portal or any content(s) therein is neither designed to support, nor replace, the relationship that exists between a patient/site visitor and his/her physician. Your use of the WebmedCentral site and its contents is entirely at your own risk. We do not take any responsibility for any harm that you may suffer or inflict on a third person by following the contents of this website.