

SYSTEMIC CANDIDIASIS AND HIV DISEASE



ways to prevent and treat fungal
infections throughout the body

A PUBLICATION FROM

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Living With HIV/AIDS

JANUARY 2005



Candidiasis is a fungal infection and among the most common conditions seen in people with HIV. While candidiasis is a rather common condition in general, it's often the first illness and sign that HIV disease is progressing to a more severe stage. Candidiasis outbreaks can be frequent, can cause great discomfort and can add to the decline of health in HIV disease.

Candidiasis can occur in the mouth, throat, windpipe (esophagus), vagina or on the skin. It can also spread throughout the body. While this is rare, it is

life-threatening. The most common places for infection are in the mouth and vagina. Recurrent and difficult to treat vaginal yeast infections are a sign of HIV disease progression in women.

This publication focuses on systemic candidiasis—when it spreads throughout the body and may impact many systems. For more information on oral or vaginal candidiasis, read Project Inform's publications, *Oral Candidiasis* and *Vaginal Candidiasis*, available at 1-800-822-7422 and www.projectinform.org.

what causes candidiasis?

The fungus called *Candida* causes candidiasis. This fungus is normally found in small amounts in the mouth, vagina, digestive tract and skin. In a healthy person, other bacteria and the immune system keep it from becoming a problem.

However, a weak immune system makes it easier for *Candida* to grow and cause infection. In HIV disease, the most serious *Candida* outbreaks occur when CD4+ cell counts are very low (below 100). In people with weak immune systems, candidiasis can recur and be difficult to treat.

Factors including diabetes, pregnancy, iron, folate, and vitamin B12 or zinc deficiency, and use of antihistamines can increase the risk of *Candida* infections. Things that may weaken the immune system—from chemotherapy to stress and depression—can also cause or worsen candidiasis.

Infection in the vagina

Vaginal candidiasis, called yeast infection or vaginitis, is an infection of the vulva and/or vagina. It causes a smelly, thick, white-yellow discharge that might occur with itching, burning and swelling. A bad case can make walking, peeing or sex very painful.

Infection in the mouth

Oral candidiasis, called *thrush*, involves the mouth and sometimes the throat. It can also occur without symptoms. The most common symptoms usually include discomfort of the mouth and throat, burning and an altered sense of taste (often described as “bad”). Creamy white or yellowish coatings or spots on the mouth and throat are also common. Thrush is rare if a person’s CD4+ cell count is above 500, but outbreaks are more common as it drops to 100.

Infection in the throat

Candidiasis of the throat and windpipe, called esophageal infection, is a serious condition. It is on the list of AIDS-defining illnesses, affecting up to 1 in 5 people with AIDS. It often occurs together with thrush. Symptoms include chest pain, nausea and pain when swallowing. The esophagus may become partly blocked by coatings and spots that build up. In rare cases, bad ulcers can rupture the

esophagus. Esophageal candidiasis can spread, or *disseminate*, into the stomach and intestines.

Because esophageal candidiasis can make swallowing painful, people may not eat enough and lose weight if it’s not treated promptly.

Infection of the skin

Candida can infect skin in the armpits, groin (including the scrotum and tip of the penis in men) and under the breasts. This is called *cutaneous* candidiasis. Infection can also occur around burns, cuts or catheters. It causes a bright red uneven eruption in the folds of skin. This may be coated by a white, wrinkled layer of tissue. Other symptoms include a mild burning. Fingernails and toenails can also be infected, which can be a special problem for people whose hands are often in water, like bartenders or dishwashers.

Infection throughout the body

Systemic candidiasis is when *Candida* spreads throughout the body, and it can be life-threatening. Infection might include the brain, heart, kidneys, eyes, liver, genital tract and joints. This form occurs most often in people with low white blood cell counts (*neutropenia*). This type of infection is also called *disseminated* candidiasis.

Diagnosis

Oral, vaginal and skin infections are usually diagnosed by appearance and symptoms. Lab tests are usually performed if the infection does not clear up after treatment.

If a person with thrush has problems swallowing (food “gets stuck”) and/or has bad chest pain, he or she may also have esophageal infection. If symptoms do not improve with treatment, or if someone has problems swallowing but does not have thrush, an *endoscopy* is usually performed. This is when a doctor uses a small tube to look into the esophagus.

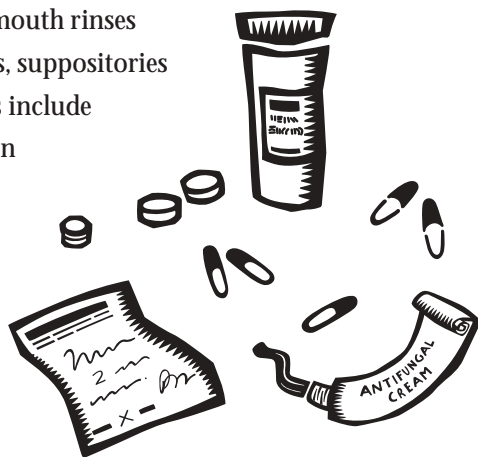
Systemic candidiasis is very difficult to diagnose. *Candida* in the blood may come from a local infection (like the mouth or site of a catheter) as well as from infection of internal organs. *Candida* may only briefly be present in the blood when an internal organ is infected, therefore a blood test result is not always reliable.

Treatment

Many drugs are used to treat candidiasis, and they come in two types: *topical* (active only where it’s applied) and *systemic* (active throughout the body). Choice of therapy depends on where the infection is and how severe the symptoms are. Topical treatment is the first choice for oral, vaginal or skin infections, and it generally works for mild-to-moderate cases. If topical drugs do not work, or if outbreaks occur often, systemic drugs may be needed. Systemic treatment is always used for esophageal or disseminated disease.

Topical therapy

Topical therapy includes mouth rinses or lozenges, vaginal tablets, suppositories and creams. Topical drugs include amphotericin B suspension (Fungizone), clotrimazole (Lotrimin), econazole (Spectazole), ketoconazole (Nizoral), miconazole (Monistat) or nystatin (Mycostatin).



Mouth rinses

Mouth rinses are less effective as they only have contact with the mouth for a short time. However, they may be the best choice for someone with a very sore or dry mouth. Rinses are held in the mouth for as long as possible and should be swilled around and then swallowed. They are used at least four times a day and continued for a few days after the symptoms have gone. The most widely used rinse is nystatin (Mycostatin Oral Suspension).

Lozenges

For oral symptoms, one or two lozenges or *troches* are taken 3–5 times a day. They should be sucked slowly and not chewed or swallowed whole. Common brands are clotrimazole (Mycelex) and nystatin (Mycostatin).

Creams and ointments

Creams and ointments are used for skin and nail infections. They can be used at the corners of the mouth or rubbed into affected areas of skin, including the labia. They should be applied 2–4 times a day by gentle and thorough massage. The length of therapy varies, but it often takes 10–20 days and should continue for a few days after the symptoms clear up.

Products include amphotericin B (Fungizone), clotrimazole (Lotrimin), clotrimazole plus a steroid (Lotrisone), miconazole (Monistat-Derm), clotrimazole (Mycelex), nystatin plus a steroid (Mycolog-II), nystatin (Mycostatin), ketoconazole (Nizoral) and econazole (Spectazole). Creams containing a steroid should not be used for children under 12. Some creams can be bought over the counter and as a prescription. Over-the-counter products are usually labeled for treating athlete’s foot or jock itch.

Vaginal suppositories

Vaginal suppositories or tablets are put into the vagina once only clotrimazole or once a day for three days miconazole. Common brands are GyneLotrimin and Mycelex-G (clotrimazole) and Monistat 3 (miconazole). A single oral dose of fluconazole (Diflucan) is increasingly used for treating vaginal candidiasis.

systemic therapy

Systemic treatments are used for esophageal and disseminated candidiasis. They can also be used for other infections that recur often or do not clear up with topical treatment.

Ketoconazole

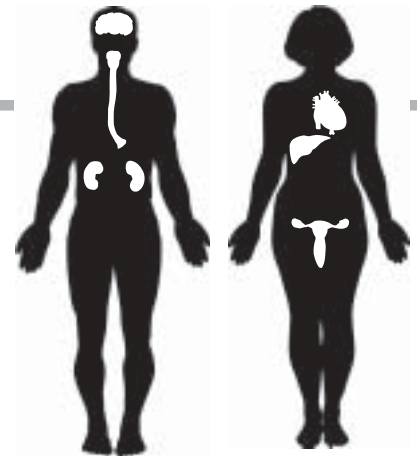
Ketoconazole (Nizoral) is taken at 200 or 400mg once a day. It needs acid to be absorbed, so it should be taken with food. Antacids should be avoided. It should also not be taken at the same time as other therapies that may contain a buffer or antacid, like didanosine (ddI, Videx). It may not be well absorbed in people with gut problems or who cannot eat very much. Taking it with an acidic drink like a cola may help.

Fungizone

Fungizone (amphotericin B) is given directly into a vein. It's used to treat disseminated candidiasis when other systemic therapies fail or the infection is very aggressive. It is sometimes used with another drug, flucytosine, to treat specific fungal infections like cryptococcal infections.

This used to be the standard treatment for systemic or serious fungal infections. It lasted 8–12 weeks and often gave severe side effects, like kidney damage and anemia. People are now usually given amphotericin B until they start to improve (usually two weeks). They are then switched to fluconazole at 200–400mg per day.

Other forms of amphotericin B are used when systemic infections become resistant or less responsive to standard therapy. These include amphotericin B colloidal dispersion (ABCD, Amphotec) and amphotericin B lipid complex (ABLC, Abelcet). These might have fewer side effects than standard amphotericin B, but all of them can be quite toxic.



systemic infection can occur in the brain, esophagus, kidneys, heart, liver and genital tract

Fluconazole

Fluconazole (Diflucan) is taken at 200mg the first day, then 100mg once a day thereafter. Treatment typically lasts two weeks for oral or skin candidiasis and three weeks for esophageal infection (or two weeks after symptoms clear up, whichever is longer). The dose may be increased to 400mg per day if the lower dose does not work.

Studies suggest that fluconazole is more effective than ketoconazole. Some doctors still prefer to treat aggressive fungal infections with other drugs, like ketoconazole, in order to save the potent fluconazole for later use, if necessary. Resistance to fluconazole is well documented. Once it develops, then treatment options are very limited.

Itraconazole

Itraconazole (Sporanox) appears to be at least as potent as ketoconazole and may be as good as fluconazole. It needs stomach acid to be absorbed, so it should be taken with food. The dose is 200mg per day. If not enough drug is being absorbed, blood levels may need to be checked so the dose can be increased.

Itraconazole oral solution is more effective and puts higher levels of the drug in the blood than the capsule. There is a great potential for interactions between itraconazole and many anti-HIV drugs. For more information, read Project Inform's publication, *Drug Interactions*.

side effects

Topical treatments

Topical creams and ointments may cause mild burning. Some people are highly sensitive and may have a widespread skin reaction with blisters and peeling. Some creams also contain a steroid to reduce inflammation that may cause itching, irritation or dryness. Vaginal tablets do not often cause problems, but in a few women they may lead to vaginal burning or itching or skin rash. Some women experience cramps or headaches.

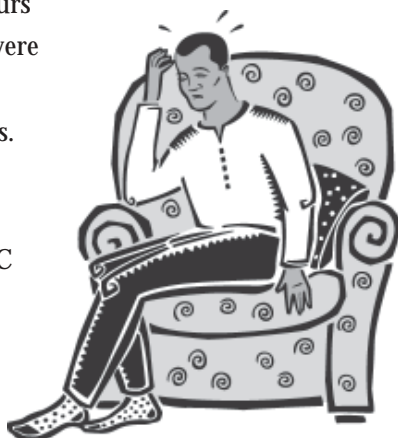
Clotrimazole lozenges may cause minor changes in liver function, but this may not require stopping the drug. Oral irritation and nausea are rare side effects of nystatin lozenges. Nystatin oral rinse (Mycostatin) is nearly non-toxic, but it may cause gut problems if excessive doses are taken.

Systemic treatments

Side effects for the oral *azole* drugs are similar, but some studies show they're more common with itraconazole. The most common are nausea, vomiting and belly pain. Others include headaches, dizziness, drowsiness, fever, diarrhea, rash and changes in taste. The most serious problem is liver toxicity, but this is rare and usually reverses after the drug is stopped. Nevertheless, liver function should be checked closely, particularly with ketoconazole.

Amphotericin B has many side effects, some quite severe. Therefore, it is only used in cases when there's a direct threat to life or all other treatments have failed. Main side effects include kidney side effects and low red blood cells (*anemia*). Others include fever, chills, changes in blood pressure, changes in appetite, nausea, vomiting and headache.

These reactions occur 1–3 hours after an infusion, are most severe with the first few doses, and diminish with later treatments. Side effects are generally the same with all amphotericin drugs, though ABCD and ABLC may be slightly less toxic.



Drug interactions

There are no known drug interactions for any topical treatment. The oral *azole* drugs have similar drug interactions.

- Anyone taking the antihistamines terfenadine (Seldane) or astemizole (Hismanal) or the anti-reflux drug cisapride (Propulsid) SHOULD NOT take ketoconazole or itraconazole and should probably avoid fluconazole. These drugs can interact to give serious heart problems.
- *Azole* drugs should not be taken with the sedatives triazolam (Halcion) or midazolam (Versed) as this could lead to dangerous levels of sedation.
- When taken with the blood-thinning agent warfarin, *azole* drugs can make the blood clot more slowly, so clotting time should be monitored.
- Taking *azoles* with oral hypoglycemic drugs may result in severe hypoglycemia, so blood sugar (glucose) levels should be checked carefully.
- Other drug interactions may occur. More details can be found in Project Inform's publication, *Drug Interactions*, and from your pharmacist.

preventing fungal infections naturally

There is a strong connection between what you eat and the health of your immune system. Nevertheless, nutritional ways to prevent and treat conditions like candidiasis are complicated and controversial. While there isn't a magic recipe that prevents or treats yeast infections in everyone, following some basic guidelines may lower your risk of yeast becoming a problem.

Most nutritionists agree that sugar, yeast, dairy, wheat, caffeine, nicotine and alcohol are the main culprits because they help yeast to grow. To prevent this, they recommend eating as little as possible of these types of foods.

Another approach is to eat larger amounts of foods that may keep yeast from growing. For example, some nutritionists believe garlic has natural antifungal properties that may help prevent candidiasis. Fresh garlic is considered best, although commercial garlic "pills" help reduce the odors. Fresh garlic can be mixed into other foods, eaten raw (up to six cloves a day), or minced and put into empty gelatin capsules. (NOTE: It's unknown if large amounts of garlic interfere with anti-HIV therapies, but it may increase the risk of side effects from using ritonavir [Norvir].)

Another factor that can contribute to uncontrolled yeast growth is using antibiotics. "Friendly" bacteria are found naturally in the body and establish a healthy balance while eliminating unfriendly yeasts. Many common antibiotics, like tetracycline and penicillin, kill these bacteria which then allow yeast to grow, especially in the vagina. It is not unusual, even for people with healthy immune systems, to experience a fungal infection after using antibiotics.

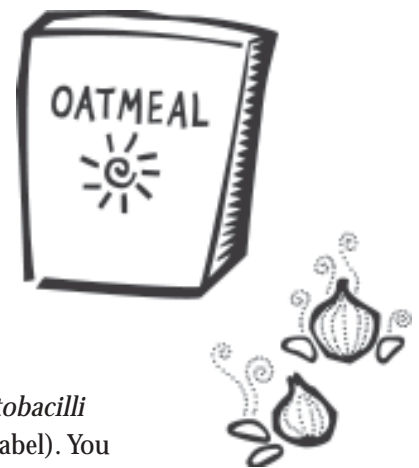
In order to lessen this effect from antibiotics and promote healthy bacteria in general, many nutritionists

recommend adding *Lactobacilli acidophilus* bacteria to your diet. It can be found in yogurts and certain milks (look for *Lactobacilli acidophilus* on the label). You can also take it in pill form, available at many health food stores.

Oral candidiasis can change how you taste and enjoy foods. It can also make eating and swallowing difficult. Avoiding acidic, spicy or hot foods as well as cigarettes, alcohol and carbonated drinks may help. All of these can irritate the insides of your mouth. Soft, cool and bland foods (like oatmeal, mashed beans, apple sauce, etc.) are recommended.

Liquid food supplements are often used to ease mouth infections and/or for weight maintenance. Remember supplements are not intended to replace solid foods. Many of these are high in sugars, which can help yeast grow. If you use supplements, make sure they contain mainly complex carbohydrates, are high in protein and have low-to-moderate sugar levels. For more information on food supplements, read Project Inform's publication, *Maintaining Weight and Nutrition*, available at 1-800-822-7422 or www.projectinform.org.

Overall, the best way to naturally prevent fungal infections is to eat healthfully and regularly, avoid excessive sugar intake and avoid or decrease alcohol and cigarettes.



tips for preventing candidiasis

- Decrease or avoid sugars (corn and maple syrup, glucose, fructose and sucrose). Sugar is food for *Candida* and helps it grow. Read the labels on packaged foods for these sugars.
- Decrease or avoid alcohol. Alcohol converts to sugar and helps *Candida* grow.
- Drink milk or eat yogurt that contains *acidophilus* bacteria—"friendly" bacteria that helps your body fight off "unfriendly" germs, like *Candida*.



the problem of antifungal resistance

Candidiasis that fails to respond to treatment has been increasingly reported, especially among people who have not benefited from fluconazole and other *azole* drugs. This is partly due to the widespread, long-term use of *azoles* for treating and preventing candidiasis. Other factors include treatment with anti-TB drugs, treatment with ciprofloxacin (Cipro) and CD4+ cell counts below 50.

Resistance to *azole* drugs has often required using amphotericin B. While potent and effective, amphotericin B is toxic, especially to the kidney. Newer versions, such as ABLC, Ambisome and Abelcet, have proven less toxic to the kidneys than the earlier formula. Moreover, a recent study comparing the earlier form to ABLC found that people tolerated ABLC better, which improved their ability to take the drug until the fungal infection successfully cleared. Even among people with some underlying kidney disease, ABLC was better tolerated, resulting in only very small changes in kidney function tests.

Nevertheless, recent studies show that exposure to *azole* treatment decreases the antifungal activity of amphotericin B. This will likely be the case for newer, less toxic forms of the drug; but more studies need to confirm this. Two other drugs have also been shown to be active against *azole*-resistant candidiasis. Voriconazole (Vfend) was recently approved in May 2002 and was shown enhanced activity against fluconazole-resistant candidiasis. Based on clinical trial data, dosage requirements are 200mg twice daily or 3–6mg/kg intravenously every 12 hours. Another drug called caspofungin acetate (Cancidas) has also shown activity against *azole*-resistant strains of candidiasis. Recommended dosage is 50mg/day.

There are drug interactions that have been observed including those with anti-HIV drugs, specifically efavirenz (Sustiva), nelfinavir (Viracept) and nevirapine (Viramune). The recommendation is to increase the daily dose to 70mg if a person is taking any of these anti-HIV drugs.

Because of antifungal drug resistance, using drugs to *prevent* fungal infections is approached with great caution and is generally discouraged. For example, when fluconazole is used to prevent these infections and resistance develops, treating newer and more aggressive infections is difficult and often unsuccessful. So keeping the antifungal drugs for treatment is generally a more desirable approach. Some people with recurrent infections do remain on long-term therapy to prevent them. In this case, however, resistance still remains a concern.

antifungal drugs and pregnancy

The Federal Guidelines for the Prevention of Opportunistic Infections include recommendations about using antifungal drugs during pregnancy. In short, they recommend that oral *azole* drugs (including fluconazole, itraconazole and ketoconazole) not be started during pregnancy. The Guidelines further state that *azoles* be stopped in women who become pregnant and that women taking these drugs use effective birth control.

In animal studies, using itraconazole or ketoconazole during pregnancy caused birth defects. There have also been four known infants born with severe skeletal problems to women who used fluconazole for an extended time while pregnant. It's presumed that these same risks apply to other oral *azole* drugs.

For treating or preventing oral or vaginal candidiasis, topical therapies like nystatin (Mycostatin, Peditri) may be preferable for pregnant women. For treating or preventing other fungal infections, like histoplasmosis, the Guidelines suggest amphotericin B, especially in the first trimester. It is also approved for treating thrush.

Although no formal studies have been performed, pregnant women have used amphotericin B without apparent harm to their unborn children. While amphotericin B may be preferable to *azole* therapy in pregnant women, it has possible severe side effects, including kidney toxicity and anemia.



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candidiasis chart

Type	Common Symptoms	Diagnosis	Treatment	Prevention
<i>Oral (thrush)</i> affects mouth and throat; usually occurs at CD4+ cell counts below 300	Discomfort, burning of mouth and throat; changed sense of taste; creamy white or yellowish patches on mouth or throat.	By appearance and symptoms. Lab tests are used if the infection does not clear after treatment.	Mouth rinses (nystatin, Mycostatin). Lozenges (nystatin, Mycostatin; clotrimazole, Mycelex). Capsules (fluconazole, Diflucan 100mg/day or itraconazole, Sporanox 200mg/day)	Maintain good oral/dental hygiene. Avoid smoking and excess sugar. Weekly fluconazole.
<i>Vaginal (vaginitis, yeast infection)</i> affects vagina and/or vulva	Odorous, white-yellow, creamy discharge with burning, swelling and itching.	By appearance and symptoms. Lab tests are used if the infection does not clear after treatment.	Vaginal creams or suppositories (clotrimazole or miconazole). Fluconazole oral tablets.	Avoid douching and scented laundry soap, bleach and fabric softeners. Avoid washing vaginal area with deodorant soaps. Wear loose fitting clothing and cotton underwear. Weekly fluconazole.
<i>Esophageal</i> affects the esophagus (feeding tube); usually occurs at CD4+ cell counts below 100	Chest pain, nausea and painful swallowing. Usually occurs with oral candidiasis.	Examination of oropharynx; endoscopy; culture and histology.	Ketoconazole (Nizoral) 200 or 400mg/day or Fluconazole (Diflucan) at 200mg once a day.	If more than one case has occurred, fluconazole preventive therapy may be warranted, particularly at low CD4+ cell counts.
<i>Skin</i> (usually affects skin in armpits, groin and under breasts)	Bright red, uneven eruption in the folds of skin that may be coated with a white membrane; mild burning feeling.	By appearance and symptoms. Lab tests are used if the infection does not clear after treatment.	Creams or ointments applied 2–4 times/day. Products include clotrimazole, nystatin, ketoconazole, miconazole, econazole and amphotericin B.	Keep skin dry.
<i>Systemic</i> (affects organs throughout body)		Can be difficult to diagnose.	Amphotericin B (Fungizone) orally or intravenously.	