

Cryptococcosis: A Winnable Battle

What is *Cryptococcus*?

Cryptococcus is a fungus that is found in soil all over the world, which produces spores that can be inhaled. *Cryptococcus* can cause a life-threatening infection called cryptococcosis, which begins as a respiratory infection and leads to cryptococcal meningitis when left untreated.

Who does *cryptococcosis* affect?

Cryptococcosis is a leading cause of death among HIV/AIDS patients and the most common cause of adult meningitis in most regions of Africa (1). The disease also affects other groups of immunocompromised patients such as cancer patients and transplant patients. Recently, there have been several cases reported where immuno competent individuals contracted cryptococcosis, yet the disease primarily affects people with weakened immune systems (2).

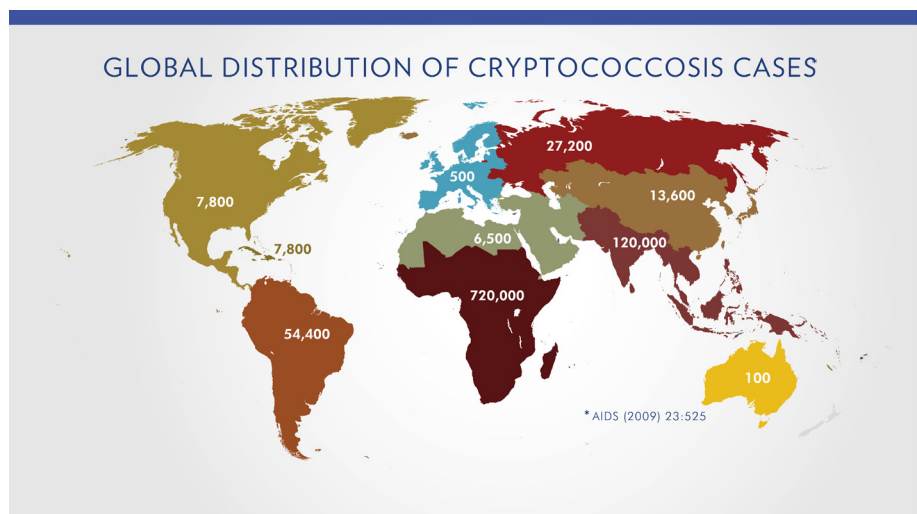
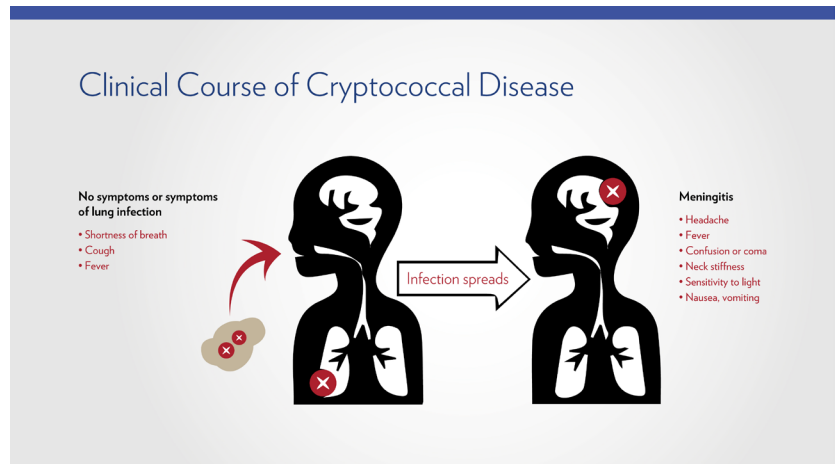
How bad is *cryptococcosis*?

Cryptococcosis kills over 600,000 people every year. This equates to one person every minute (3).

Can *cryptococcosis* be treated?

Cryptococcosis can be treated with prescription antifungal medication, and like many infections, treatment has been proven to be much more effective when therapy begins early in the disease course. In fact, the survival rate drops to 45% when the disease reaches the meningitis stage; therefore, it is imperative to diagnose patients early in the disease course (4).

Through the Diflucan Partnership, Pfizer has committed to provide antifungal medication to treat cryptococcal meningitis free-of-charge to government and nongovernmental organizations in developing countries with greater than 1% HIV and AIDS prevalence (5).



The Current Solution: Treat Cryptococcal Meningitis Patients

Nearly all HIV/AIDS programs in Africa and Southeast Asia concentrate solely on treating cryptococcal meningitis patients. Most patients at this stage of the disease are considered fatal. However, if they do survive, they can have permanent neurological damage (6).

The focus is solely on patients who are at the debilitating stage of the disease, when therapy is least effective.



The New Solution: Treat Asymptomatic Cryptococcal Antigen Positive Patients

HIV/AIDS programs need to diagnose cryptococcosis as soon as possible through cryptococcal antigen testing. It is possible to diagnose the disease before any symptoms present themselves. If the focus shifts to treating patients at the earlier stages of the disease, then therapy will be much more successful, and the likelihood of a full recovery will be increased immensely.

Comparing the Old and the New



70% of patients with cryptococcal meningitis are unable to work after one month. Their neurocognitive function is significantly impaired, and it usually takes around one year until they are back within population norms. Hospitalization costs for these patients are considerable as the average cryptococcal meningitis patient will be in the hospital for 15 days (David Boulware, personal communication, March 2013).

Around 90% of asymptomatic cryptococcal antigen positive patients are able to remain working while receiving treatment for cryptococcosis and are able to avoid hospitalization all together (David Boulware, personal communication, March 2013).

The survival rate for this patient population is 80%-- a considerable increase compared to the survival rate of cryptococcal meningitis patients, which is only 45% (4).



How to Implement the New Solution

FIRST: Adopt the CrAg LFA for diagnostic use

The current methodologies used to diagnose cryptococcosis are inadequate:



Culture – The time to results for this method is very unrealistic. It takes a minimum of 3 days, and possibly up to one month to determine if a patient is positive or negative for cryptococcosis with this method (7).



India Ink – The India Ink method has been around for decades, and while it has excellent specificity, this method has very poor sensitivity at 50%. Additionally, to perform an India Ink test, a patient must have a lumbar puncture (spinal tap) performed, which is a very invasive medical procedure that can lead to further complications (7).

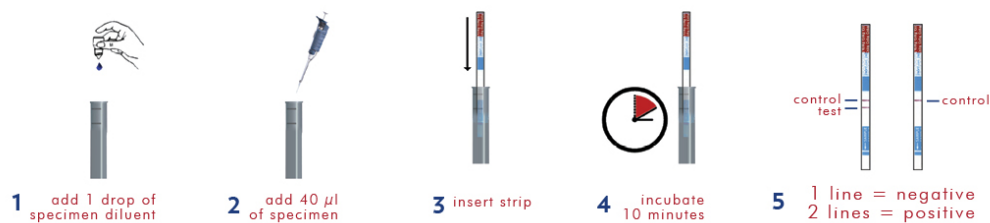


Antigen detection through latex agglutination – Antigen detection has widely been considered the best diagnostic for cryptococcosis. The vast majority of HIV programs are using the latex agglutination method to detect cryptococcal antigen. However, the latex agglutination method is not ideal for resource-limited settings for the following reasons:

- Procedure is difficult
- Requires a refrigerator and a freezer for storage
- Requires moderate laboratory infrastructure

The CrAg LFA is the ideal diagnostic for cryptococcosis because it is Rapid and Reliable.

The CrAg LFA has been found to be the most accurate diagnostic test available for cryptococcosis (8). It only takes 10 minutes to perform, and the procedure is extremely simple—it is very similar to a home pregnancy test.



“Given the superior performance, low cost, and comparatively low technological needs of the LFA for serum and CSF specimens, incorporating the cryptococcal antigen LFA in laboratory settings should be prioritized in settings with an increased prevalence of cryptococcosis. Last, consideration should be given to establishing the cryptococcal antigen LFA as the current gold standard for the detection of cryptococcal infection” (8). -Dr. Tom Chiller, CDC – Medical Laboratory Observer, March 2013

According to the World Health Organization’s Rapid Advice for Cryptococcal Infection, which was released in 2011, the CrAg LFA was said to have several advantages over the latex agglutination assay. These advantages include a rapid 5-15 minute turnaround time, little training required for use and interpretation of results, and the LFA is stable at room temperature. The document also mentioned that the LFA can be performed with minimal lab infrastructure, and it satisfies most of the WHO ASSURED criteria for point-of-care tests (9).

The CrAg LFA is the only cryptococcal antigen diagnostic that can be used on all of the specimen types shown below.



The CrAg LFA is FDA-cleared for use on serum and CSF, CE Marked for use on serum, CSF, and plasma. It has recently been evaluated for use on urine and whole blood specimens. In a preliminary study using the CrAg LFA on whole blood finger prick samples, the CrAg LFA was found to be 99% sensitive 100% specific (10).

Once the CrAg LFA is adopted for diagnostic use, the focus must shift to cryptococcosis prevention.

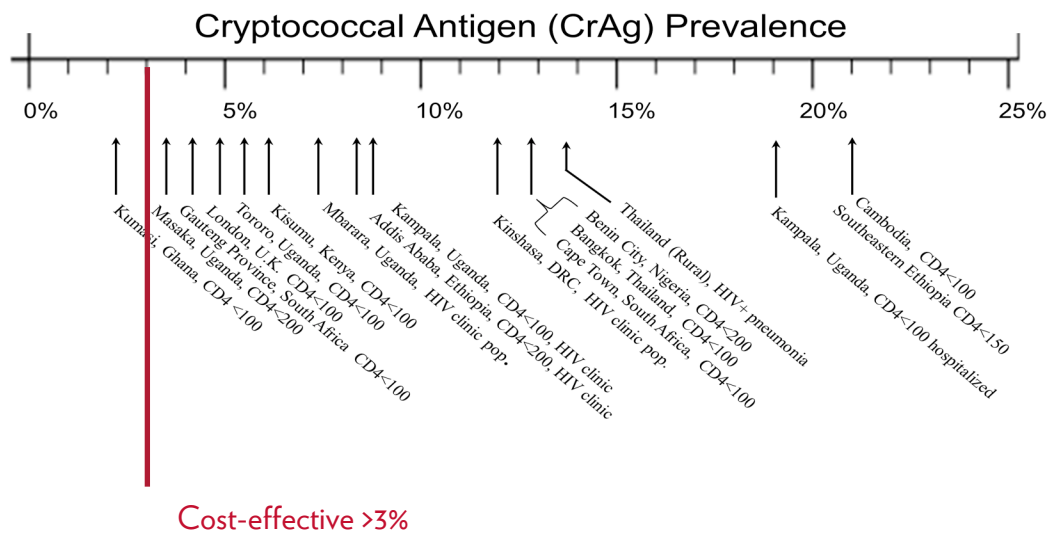
SECOND: Screen low CD4 count patients for cryptococcal antigen

To prevent patients from reaching the debilitating and fatal stages of cryptococcosis, HIV/AIDS programs need to screen all low CD4 count patients for cryptococcal antigen.

Cost effectiveness of screening patients

The first question that has to be raised about a screening program is whether or not the program is cost-effective. Screening low CD4 count patients with the CrAg LFA has been proven to be a cost-effective strategy when the prevalence of cryptococcal antigen is >3% in the patient population (11).

The graphic below represents the known prevalence of cryptococcal antigen in several different countries and patient populations (12):



Using the CrAg LFA in a screening program leads to considerable savings when compared to screening with the latex agglutination method. If the prevalence of cryptococcal antigenemia is around 8% in a given population, it would cost \$28.37 to detect once case of asymptomatic cryptococcal disease—this is a fraction of the cost compared to using the latex agglutination method, which would cost \$190.00 to detect one case (13).

The costs associated with diagnosing cryptococcosis will increase in a screening program, but these costs are off-set by avoiding hospitalization costs and reducing the amount of drugs that need to be used.

The cost-effectiveness of screening for cryptococcal antigen was evaluated by the National Health Laboratory Services (NHLS) in South Africa. The following data was presented at the AIDS 2012 Conference by Professor Wendy Stevens of the NHLS (14).

480,000	→	\$5.38	=	\$2,582,400
Number of CD4 specimens <100 per year		Cost of performing a CrAg LFA test (includes labor and overhead)		Estimated annual cost of national screening program
8,330	→	\$2,161	=	\$18,001,130
Number of CM cases per year		Cost of hospitalization for CM patient		Estimated annual cost of current CM management
4,800	→	\$2,161	=	\$10,372,800
Number of preventable CM cases per year		Cost of hospitalization for CM patient		Estimated annual savings from national screening program

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