PLoS one

Cost-Effectiveness of Primary Prophylaxis of AIDS Associated Cryptococcosis in Cambodia

Romain Micol[1,2]*[¤], Ayden Tajahmady[3], Olivier Lortholary[4,5], Suna Balkan[6], Catherine Quillet[6], Jean-Philippe Dousset[7], Hak Chanroeun[8], Yoann Madec[1], Arnaud Fontanet[1], Yazdan Yazdanpanah[9,10]

1 Unité d'Epidémiologie des Maladies Emergentes, Institut Pasteur, Paris, France, 2 Laboratoire de Virologie, Université Paris Descartes EA 36-20, Hôpital Necker-Enfants Malades, Paris, France, 3 Mission nationale d'expertise et d'audit hospitaliers, Paris, France, 4 Institut Pasteur, Centre National de Référence Mycologie et Antifongiques, Unité de Mycologie Moléculaire, CNRS URA3012, Paris, France, 5 Université Paris Descartes, Service des Maladies Infectieuses et Tropicales, Centre d'Infectiologie Necker-Pasteur, Hôpital Necker-Enfants Malades, Paris, France, 6 Médecins Sans Frontières, Paris, France, 7 Médecins du Monde, Hopital Kosamak, Phnom Penh, Cambodia, 8 Service des Maladies Infectieuses, Hopital Calmette, Phnom Penh, Cambodia, 9 Avenir-ATIP Unit, INSERM U995, Paris, France, 10 Service Universitaire des Maladies Infectieuses et du Voyageur, CH Tourcoing, Faculté de Médecine de Lille, Lille, France

Abstract

Background: Cryptococcal infection is a frequent cause of mortality in Cambodian HIV-infected patients with CD4+ count ≤100 cells/μl. This study assessed the cost-effectiveness of three strategies for cryptococcosis prevention in HIV-infected patients.

Methods: A Markov decision tree was used to compare the following strategies at the time of HIV diagnosis: no intervention, one time systematic serum cryptococcal antigen (CRAG) screening and treatment of positive patients, and systematic primary prophylaxis with fluconazole. The trajectory of a hypothetical cohort of HIV-infected patients with CD4+ count ≤100 cells/μl initiating care was simulated over a 1-year period (cotrimoxazole initiation at enrollment; antiretroviral therapy within 3 months). Natural history and cost data (US$ 2009) were from Cambodia. Efficacy data were from international literature.

Results: In a population in which 81% of patients had a CD4+ count ≤50 cells/ μl and 19% a CD4+ count between 51–100 cells/μl, the proportion alive 1 year after enrolment was 61% (cost $ 472) with no intervention, 70% (cost $ 483) with screening, and 72% (cost $ 492) with prophylaxis. After one year of follow-up, the cost-effectiveness of screening vs. no intervention was US$ 180/life year gained (LYG). The cost-effectiveness of prophylaxis vs. screening was $ 511/LYG. The cost-effectiveness of prophylaxis vs. screening was estimated at $1538/LYG if the proportion of patients with CD4+ count ≤50 cells/μl decreased by 75%.

Conclusion: In a high endemic area of cryptococcosis and HIV infection, serum CRAG screening and prophylaxis are two cost effective strategies to prevent AIDS associated cryptococcosis in patients with CD4+ count ≤100 cells/μl, at a short-term horizon, screening being more cost-effective but less effective than prophylaxis. Systematic primary prophylaxis may be preferred in patients with CD4+ below 50 cells/μl while systematic serum CRAG screening for early targeted treatment may be preferred in patients with CD4+ between 51–100 cells/μl.

Introduction

In industrialized countries, fluconazole prophylaxis is not cost-effective to prevent primary systemic fungal infections in AIDS (acquired immune deficiency syndrome) patients because of the low incidence of these infections [1,2,3]. Cryptococcosis is one of the most frequent and most serious opportunistic infections (OI) in AIDS patients in developing countries [4,5,6]. The current global

burden of cryptococcal meningitis represents 957,900 cases each year resulting in 624,700 deaths during the first 3 months after infection [7]. Prevention of this opportunistic infection is a very important public health issue in developing countries [8]. In Cambodia, cryptococcosis was the leading cause of mortality among hospitalized AIDS patients in the 1990s [9,10]. In four recent studies involving severely immunosuppressed patients with CD4+ count <100 cells/μl initiating combination antiretroviral

therapy (cART), the prevalence of positive serum cryptococcal antigen (CRAG) was 20.2% (57/282) in Cambodia in 2004, 13.0% (42/336) in South Africa from 2002 to 2005, 8.8% (26/295) in Uganda during 2004–2006 period, and 12.9% (11/85) in Thailand [11,12,13,14]. These studies provided evidence that systematic screening for serum CRAG was a clinically valuable strategy for early detection and targeted pre-emptive antifungal treatment. In addition, in another study performed in rural Uganda, asymptomatic positive serum CRAG was found to be an independent predictor of death during the first 12 weeks of cART in individuals with advanced HIV disease [15]. Cambodian health authorities currently recommend systematic primary prophylaxis with fluconazole in HIV-infected patients with CD4+ count <100 cells/µl (i.e. 200 mg/day orally) [16]. In 2009, the monthly cost of generic fluconazole was US$ 1.16. The cost of one time capsular cryptococcal polysaccharide detection was US$ 6.6. The aim of this study was to assess the cost-effectiveness of systematic primary prophylaxis with fluconazole (200 mg/day) or systematic serum CRAG screening and targeted treatment of positive cases compared to no intervention in HIV-infected patients with CD4+ count ≤100 cells/µl in Cambodia.

Methods

Analytic review

First order Monte Carlo simulation of a Markov transition model was used to project disease progression in patients with CD4+ count ≤100 cells/µl presenting to care, excluding patients with symptomatic cryptococcal meningitis. The course of the disease was modeled for one hundred thousand hypothetical HIV-infected individuals for 12 months after presentation to care. The time-horizon was therefore one year. Based on the Cambodian recommendations, it was assumed that all severely immunosuppressed patients initiated combination cART within three months after detection of HIV seropositivity. Pneumocystis jirovecii prophylaxis with cotrimoxazole was systematically administered to all patients. The patient trajectories with each of the following three strategies were evaluated at the time of HIV diagnosis and clinic enrollment: (1) no intervention in relation to cryptococcal prevention (comparator), (2) systematic primary prophylaxis with fluconazole 200mg/day for 6 to 12 months unless CD4+ count increased to more than 100 cells/µl, and (3) systematic serum CRAG screening and early targeted treatment of positive asymptomatic patients with fluconazole 200 mg/day after systematic lumbar puncture for 3 months. Asymptomatic serum CRAG was defined as positive serum CRAG detection with no pulmonary cryptococcosis, no symptom suggestive of meningoencephalitis (i.e. no neck stiffness, no altered mental status and no neurologic deficit), negative CRAG detection in cerebrospinal fluid, negative India ink staining in cerebrospinal fluid, and negative cryptococcal cultures in cerebrospinal fluid, blood, and urine. Patients responding to cART with a CD4+ count >100 cells/µl after 9 months of cART were dropped from intervention's cycle, as discontinuation of cryptococcosis prophylaxis during cART is considered in patients with CD4+ count >100 cells/µl [17,18]. These patients remained however in the model until the end of the simulation without the occurrence of a new cryptococcal infection or others OI. The performance of these strategies was evaluated using incremental cost-effectiveness analysis. Incremental cost-effectiveness ratios were calculated as the additional cost (in US$) of a specific strategy compared with the cost of the next less expensive strategy, divided by the additional gain in life expectancy (per year of life gained) for this strategy. A payer perspective was adopted, i.e. based on the costs to the health

system. Cost and effectiveness were not discounted since the follow-up period was less than 1 year. All costs and cost-effectiveness ratios were expressed as dollars (2009 US$) per year of life gained. A strategy 'A' was considered weakly dominated by another strategy 'B' when the incremental cost-effectiveness ratio of the strategy 'A' vs. the comparator (i.e. no intervention) was higher than the incremental cost effectiveness ratio of the strategy 'B' vs. the strategy 'A'. A strategy 'A' was considered strongly dominated by a strategy 'B' when this latter strategy resulted in higher effectiveness and a lower overall cost than the strategy 'A'. In addition, the performance of these strategies was estimated by determining the number needed to test and treat (i.e., with serum CRAG screening and early targeted treatment strategy) and the number needed to treat (i.e., with systematic primary prophylaxis with fluconazole) to prevent 1 death, respectively, as well as the costs associated. To estimate the cost associated to prevent 1 death, for serum CRAG screening and early targeted treatment strategy, we considered the cost of CRAG screening test and fluconazole for those tested positive. For systematic primary prophylaxis with fluconazole we considered the cost of fluconazole. We used our Markov transition model to project these costs.

Model structure

The model (**Figure 1**) characterized an individual patient's disease progression as a sequence of transitions from one "health state" to another, each corresponding to the patient's underlying true health. Health states were defined by current CD4+ count cells/µl and the efficacy of combination antiretroviral therapy. **Figure 1A** describes the course of patients with or without systematic prophylaxis, and **Figure 1B** with the CRAG screening strategy. At each state, patients could develop a cryptococcal meningitis, pulmonary cryptococcosis, or other opportunistic infections (any OI in patients with negative serum CRAG or with isolated positive serum CRAG). The incidence of these OIs was stratified based on CD4+ count categories (0–50 and 51–100 cells/µl). These OIs were assumed to lead to either death or full recovery. The development of an OI was also assumed not to influence the subsequent course of CD4+ count or the probability of a subsequent OI.

Patients responding to cART virologically were considered to have achieved successful immune reconstitution (CD4+ counts increasing over time). The CD4+ cell gain after three months was 47cells/µl, after 6 months was 47 cells/, and after 9 months was 27cells/µl in patients responding to cART. Patients non responding to cART were considered to decline their CD4+ count during follow-up [19,20]. The duration of each cycle was 3 months. The non-responder status to cART was assumed to be constant during the patient's follow-up. The initial CD4+ count and non-responder status to cART of each patient were randomly selected from given distributions. The sequence of clinical trajectories for a given patient until death or end of simulation was fully determined by a set of estimated probabilities.

Baseline characteristics and transition probabilities (Table 1)

CD4+ distributions in HIV-infected patients seen for the first time were from two highly active antiretroviral therapy access program in Phnom Penh (Prea Bat Norodom Sihanouk Hospital - program supported by Médecins Sans Frontières, and Kosamak Hospital – program supported by Médecins Du Monde) [11]: 81% of patients had a CD4+ count ≤50 cells/ µl and 19% a CD4 cell count between 51–100 cells/µl. The probability of positive serum CRAG and mortality due to cryptococcal infection were from Micol et al. study in antiretroviral therapy access programs in
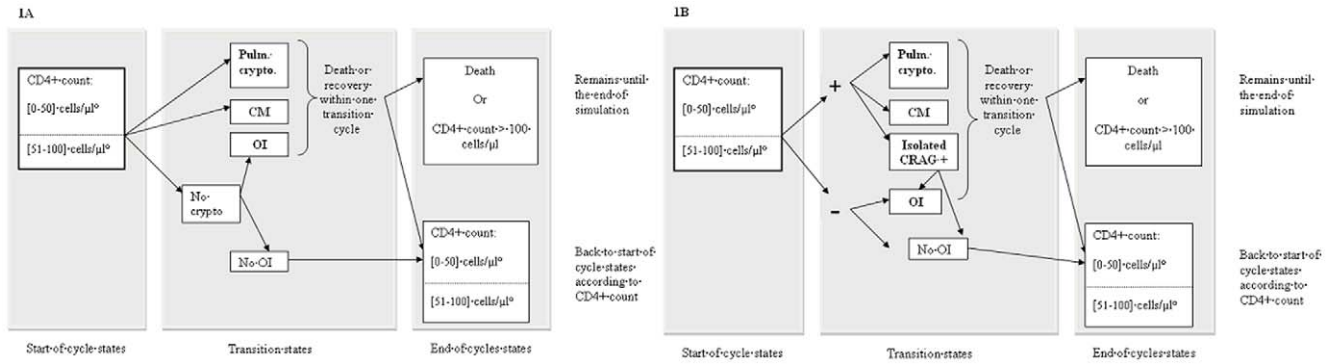
Figure 1. Model structure for no intervention or primary prophylaxis intervention (A), and CRAG screening intervention for treatment of positive cases (B). The probabilities of transition were stratified according to CD4+ count categories (0–50 and 51–100 cells/µl). At the end of one cycle (i.e., after 3 months), patient was back to start of cycle state within the same CD4 cell count strata or a higher CD4 cell count based on cART efficacy or was remaining alive in the model (without occurrence of new OI) because of death or CD4 cell count >100 cells/µl thanks to cART efficacy. Pulm. Crypto.: pulmonary cryptococcosis; CM: cryptococcal meningitis; OI: opportunistic infections other than cryptococcosis; +: positive serum CRAG screening; −: negative serum CRAG screening; Isolated CrAG+: Asymptomatic positive serum CRAG. Non-response to cART was included in the transition probabilities.
doi:10.1371/journal.pone.0013856.g001

Phnom Penh [11]. This latter study used the Latex Agglutination System (CALAS; Meridian Bioscience Europe, Nice, France). The sensitivity and specificity of the test (used in a laboratory) are 99%

and 97%, respectively [21]. All patients' data routinely entered in Fuchia v1.5 (Epicentre – MSF) from the Médecins Sans Frontières Cambodian cohort in 2004–2005 were used to calculate the risk of

Table 1. Estimates of the probabilities of events.

Variable probability	CD4+ cells/µl %		Reference
	[0–50]	**[51–100]**	
CD4+ distribution in patients attending for the first time the cART program	81	19	[11]
Probability of cART immunological efficacy after 1 year on cART	86.0	86.0	MSF database, [19]
Probability CD4+ cell increase above 100 cells/µ after 6 months of successful cART	46.0	46.0	[22]
Asymptomatic positive serum CRAG at screening	14.3	4.3	[11]
Probability of CM			MSFdatabase, [11]
Without fluconazole prophylaxis	15.4	9.1	
With fluconazole primary prophylaxis	1.0	1.0	
With fluconazole secondary prophylaxis	15.0	10.0	
With negative serum CRAG without fluconazole primary prophylaxis	0.6	0.0	
With positive serum CRAG without fluconazole primary prophylaxis	48.3	0.0	
Probability of pulmonary cryptococcosis			MSF database, [11]
Without fluconazole prophylaxis	3.1	1.8	
With fluconazole primary prophylaxis	0.1	0.1	
With fluconazole secondary prophylaxis	10.0	5.0	
With negative serum CRAG without fluconazole primary prophylaxis	0.000	0.000	
With positive serum CRAG without fluconazole primary prophylaxis	39.0	69.8	
Probability of OI other than cryptococcal infection			MSF database
For patients with negative serum CRAG	0.540	0.395	
For patients with isolated positive serum CRAG	0.540	0.395	
Probability of death			MSF database, [11]
In patients with CM	0.53	0.53	
In patients with pulmonary cryptococcosis	0.200	0.200	
In patients with another OI	0.200	0.200	

CM, cryptococcal meningitis; OI, opportunistic infections; cART, combination antiretroviral therapy; CRAG, cryptococcal antigen.
doi:10.1371/journal.pone.0013856.t001

other OIs occurrence by CD4 cell count strata [22]. Transition probabilities were stratified on two categories of CD4+ count ($\leq$50 cells/μl versus 51–100 cells/μl) and were determined for three months (probability of cryptococcal meningitis or pulmonary cryptococcosis with or without fluconazole prophylaxis, probability of others OI, probability of death). We used data from another study performed by our group in Cambodia to estimate the CD4+ count increase in patients on efficacious cART (i.e. to estimate the time that the patients remains below 100 CD4 cells/μl) [22]. In the latter study, we showed that in patients with a median (Q1–Q3) of CD4+ count at baseline at 20 cells/μl (6–78), the CD4+ count increased after cART initiation to reach median levels of 130 cells cells/μl (IQR, 87–189) at 6 months and 189 cells/μl (IQR, 135–250) at 12 months. In other studies, ART efficacy was estimated at 86% after one year on cART. In patients responding to cART the CD4+ cell gain was 47cells/μl after three months, 94 cells//μl after 6 months, and 121 cells/μl after 9 months. Patients non responding to cART were considered to decline their CD4+ count by 18.8 CD4+ cells/μl every three months [19,20]. More details about the model are available in the **technical appendix S1**.

Costs (Table 2)

Costs included direct medical costs were expressed in 2009 US$. Drugs costs were from MSF cART access programs. Cotrimoxazole *Pneumocystis jirovecii* prophylaxis cost was 0.30 $/month, fluconazole prophylaxis cost 1.16 $/month, and cART treatment 30.5 $/month. Test costs and in particular CRAG screening test (6.6 $) costs were from the manufacturer (CALAS; Meridian Bioscience Europe, Nice, France) and did include the time of human resource to perform the test. To estimate costs related to cryptococosis disease and other opportunistic disease treatment and care, we considered inpatients and outpatients stays, treatment and test costs. Inpatient costs were from Médecins Sans Frontières, outpatients costs were from Médecins Du Monde. Cryptococcal meningitis (i.e.; treated with amphotericin B for 2 weeks and fluconazole 400mg/day for 8 to 10 weeks) and others OI treatment was estimated at 62.6 $/month. Patients with pulmonary cryptococcosis (mainly a severe pneumonia) received the same treatment as the patients with cryptococcal meningitis [17].

Sensitivity analysis

One-way sensitivity analyses were performed by varying key parameters (proportions of patients with CD4+ count $\leq$50 cells/μl, cost of fluconazole prophylaxis, cost of CRAG screening, and mortality rate due to cryptococcal meningitis) over a wide range of

reasonable values to evaluate the impact of data uncertainties and to determine the robustness of the overall conclusions.

Analyses were performed with TreeAge ProTM 2006 (Williamstown, MA, USA). This study was approved by the National Ethics Committee for Health Research of the Cambodia Ministry of Health.

Results

Baseline analysis

After one year of follow-up, primary prophylaxis by fluconazole or systematic CRAG screening and treatment of positive cases were more effective (probability of being alive at twelve months = 72% and 70% respectively) and more expensive (twelve months cost = 492 $ and 483 $ respectively) than the "no intervention" strategy (61%, and 472 US$) (**Table 3**). Although the "prophylaxis strategy" was more expensive than the "screening strategy" ($ 492 vs. $ 483 over a period of twelve months), it was also more effective (probability of being alive at twelve months = 72% vs. 70%). The cost-effectiveness of "screening strategy" (= 180 $/ life year gained [LYG] vs. no intervention) was lower than the cost-effectiveness of primary prophylaxis (511 $/LYG compared to screening) (**Table 3**). Compared to "no intervention" strategy, to prevent 1 death, 10.8 persons needed to undergo CRAG screening and treatment of positive cases, and 8.9 persons needed to be treated by fluconazole prophylaxis, respectively. On the basis of the current CRAG test ($6.6/test) and fluconazole prophylaxis cost ($3.47/3 months) this translates into $77 to save 1 life with serum CRAG screening and early targeted treatment strategy and $102 to save 1 life with fluconazole prophylaxis strategy.

Sensitivity analysis

One-way sensitivity analysis was initially performed on the proportion of patients with CD4+ count $\leq$50 cells/μl attending for the first time the cART access program (**Table 4**). Results were sensitive to variations in the proportion of patients with a CD4+ count $\leq$50 cells/μl at enrollment. If the proportion of patients attending the HIV clinic for the first time with CD4+ count $\leq$50 cells/μl increased by 25% to 97.3% of the clinic population (vs. 81% in the basecase analysis), the incremental cost-effectiveness ratio of both interventional strategies decreased and especially the incremental cost-effectiveness ratio of prophylaxis vs. screening decreased to 478 $/LYG. If this proportion decreased by 50% to 40.5%, the incremental cost-effectiveness ratio of prophylaxis vs. screening increased to 733 $/LYG. Finally if this proportion decreased by 75% to 20.3%, the incremental cost-effectiveness ratio of prophylaxis vs. screening increased to 1538 $/LYG. Reducing the cost of fluconazole (from 3.47 $ to 1.74 for three months) reduced fluconazole prophylaxis cost-effectiveness ratio (from 511 to 256 $/LYG respectively) (**Table 5**). When the cost of fluconazole is free (i.e. cost of fluconazole = 0 $) such as in the Pfizer Diflucan Partnership Program [23], screening strategy is weakly dominated (i.e. screening presented a higher incremental cost-effectiveness ratio than prophylaxis that is more effective) and the incremental cost-effectiveness ratio of prophylaxis vs. no intervention decreased to 141 $/LYG. Reducing the CRAG screening test cost (from 6.6$ to 3.3, or 1.7 $) decreased the incremental cost-effectiveness ratio of screening from 180, to 137, and 116 $/LYG respectively. A reduction of the mortality rate due to cryptococcal meningitis also did not inverse the results but favored the incremental cost-effectiveness ratio of screening.

Table 2. Estimates of the costs.

Costs in 2009 US$/3 months (MSF and MDM databases)	
Cotrimoxazole *Pneumocystis jirovecii* prophylaxis	0.89
Fluconazole prophylaxis	3.47
cART	91.5
CM/Pulmonary cryptococcosis treatment and care	187.9
Other opportunistic infections treatment and care	187.9
CRAG screening test (cost per test)	6.63

cART, combination antiretroviral therapy; CM, cryptococcal meningitis; CRAG, cryptococcal antigen.
doi:10.1371/journal.pone.0013856.t002

Table 3. Cost-Effectiveness of systematic fluconazole primary prophylaxis and serum cryptococcal antigen screening.

Strategy	Cost ($)	Effectiveness* (in year)	1 year survival (%)	Cost per LYG ($/LYG)	ICER ($ incr./LYG)
No intervention	472	0.741	61	636	Reference
CRAG screening+targeted therapy	483	0.803	70	601	180.0**
Fluconazole prophylaxis	492	0.822	72	599	511.0***

$: costs in 2009 US$, LYG, life year gained; CE, cost-effectiveness; ICER, Incremental cost-effectiveness ratio.
*Effectiveness = mean life expectancy one year after HIV diagnosis and clinic enrollment.
**ICER of CRAG screening vs. no intervention.
***ICER of prophylaxis vs. CRAG screening.
doi:10.1371/journal.pone.0013856.t003

Discussion

This is the first study assessing the cost-effectiveness of three alternative prevention strategies of cryptococcal infection in HIV-infected patients. Cryptococcal opportunistic infection is highly endemic in Cambodia (estimated prevalence in HIV-infected patients with CD4+ count ≤100 cells/μl of 20.6% (58/282) in 2004 [11]) and represents more generally a significant public health burden in South East Asian AIDS patients [4,5,9,24,25]. The results of the present study suggest that, at a short term horizon of one year, the systematic CRAG screening (for targeted treatment of positive cases) in patients with CD4+ cell counts <100 cells/μl presenting to care in Cambodia, is more cost effective for cryptococcosis prevention compared to the systematic primary prophylaxis strategy. They also illustrate however that systematic primary prophylaxis strategy is more effective than systematic CRAG screening and associated with an acceptable cost-effectiveness ratio (US$ 511/LYG). Although there is no clearly defined threshold below which any health intervention can be considered to be cost-effective, the guidelines of the WHO

Commission on Macroeconomics and Health can be used to establish the comparative value of alternative interventions in a given country, taking into account its ability to pay for goods and services [26]. According to these guidelines, a strategy is cost-effective if the incremental cost-effectiveness ratio is below 3× the annual per capita Gross Domestic Product (GDP) and very cost-effective if the incremental cost-effectiveness ratio is below 1× the annual per capita GDP. The Cambodian GDP was US$ 650 in 2008 (http://www.imf.org/external/pubs/ft/weo/2007/02/weodata/index.aspx). Because the incremental cost-effectiveness ratio of systematic primary prophylaxis strategy vs. CRAG screening ($ 511) is less than the Cambodian GDP, this strategy could be considered as a very cost effective strategy to prevent AIDS associated cryptococcosis in Cambodia.

The cost-effectiveness of strategies to prevent AIDS associated cryptococcosis in Cambodia estimated in our study are comparable to the cost-effectiveness of other strategies implemented in developing countries to prevent opportunistic infections occurrence in HIV-infected patients although we recognize the need for caution in directly comparing results of cost-effectiveness analysis

Table 4. Sensitivity analyses: impact on the results of varying the proportion of patients with CD4+ count ≤50 cells/μl.

	Cost (2009 $)	Effectiveness* in years	Incremental CE ratio ($/LYG)**
Increasing the proportion of patients with CD4+ count ≤50 cells/μl by 20% (i.e. 0.9732)			
No intervention	485	0.727	
Serum CRAG screening	495	0.788	170
Fluconazole prophylaxis	506	0.811	478
Reducing the proportion of patients with CD4+ count ≤50 cells/μl by 25% (i.e. 60.75%)*			
No intervention	456	0.761	
Serum CRAG screening	468	0.824	198
Fluconazole prophylaxis	474	0.835	550
Reducing the proportion of patients with CD4+ count ≤50 cells/μl by 50% (i.e. 40.5%)			
No intervention	439	0.783	
Serum CRAG screening	450	0.838	207
Fluconazole prophylaxis	455	0.844	733
Reducing the proportion of patients with CD4+ count ≤50 cells/μl by 75% (i.e. 20.25%)			
No intervention	424	0.801	
Serum CRAG screening	437	0.858	214
Fluconazole prophylaxis	439	0.859	1538

$: costs in 2009 US$, CRAG, cryptococcal antigen.
*Effectiveness = mean life expectancy one year after HIV diagnosis and clinic enrollment.
**US$ per year of life gained.
***The proportion of patients attending the HIV clinic for the first time with CD4+ count ≤50 cells/μl is 81.2% as baseline. Thus the reduction of this latter proportion by 25% decreased this proportion to 60.75%.
doi:10.1371/journal.pone.0013856.t004

Table 5. Sensitivity analyses: impact on the results of varying the cost of fluconazole, the cost of CRAG screening test, and the cryptococcal meningitis mortality rate.

	Cost (2009 $)	Effectiveness* in years	Incremental CE ratio ($/LYG)**
Reducing the cost of fluconazole by 50% (i.e. $ 1.74)			
No intervention	470	0.741	
Serum CRAG screening	482	0.803	190
Fluconazole prophylaxis	487	0.821	256
Reducing the cost of fluconazole by 100% (i.e. $ 0.0)			
No intervention	469	0.741	
Serum CRAG screening	480	0.803	Weakly dominated
Fluconazole prophylaxis	480	0.821	141.0 (vs. no intervention)
Reducing the cost of CRAG screening test by 50% (i.e. $ 3.315)			
No intervention	472	0.741	
Serum CRAG screening	480	0.803	137
Fluconazole prophylaxis	492	0.821	678
Reducing the cost of CRAG screening test by 75% (i.e. $ 1.6575)			
No intervention	472	0.741	
Serum CRAG screening	479	0.803	116
Fluconazole prophylaxis	492	0.821	750
Reducing the cryptococcal meningitis mortality rate by 25% (i.e. 39.75%)			
No intervention	487	0.7683	
Serum CRAG screening	489	0.8111	44
Fluconazole prophylaxis	495	0.8250	446

$: costs in 2009 US$; CRAG, cryptococcal antigen;
*Effectiveness = mean life expectancy one year after HIV diagnosis and clinic enrollment;
**US$ per year of life gained.
doi:10.1371/journal.pone.0013856.t005

because of differences in study design, cost components used, and the time horizon of studies. For example, the cost-effectiveness of co-trimoxazole prophylaxis for persons at early stages of HIV infection (WHO stage > or = 2) compared to no prophylaxis has been evaluated at 150 $/LYG in Côte d'Ivoire [27] The cost-effectiveness of isoniazid preventive therapy in newly HIV-infected patients with positive tuberculin skin test has been evaluated at 102 $/QALY gained in counseling and testing centers in Kampala, Uganda [28]. In the same study, the cost-effectiveness of isoniazid preventive therapy in all newly HIV-infected patients regardless to positive tuberculin skin test has been evaluated at 106US$/QALY gained compared to the targeted testing strategy. Moreover, as far as cryptococcal infection prevention in HIV-infected patients is considered a recent study in Uganda showed that initial CRAG screening prior to starting ART in patients with CD4+ count ≤100 cells/μl is cost-effective; the number of patients needed to test and treat with CRAG screening and fluconazole to save 1 life was estimated 15.9 and the costs at $266 [13]. Systematic primary prophylaxis strategy was not evaluated in this study.

In this Cambodian analysis we found that a decrease in the proportion of patients with CD4+ count ≤50 cells/μl significantly impacted the incremental cost-effectiveness ratio of screening and prophylaxis strategies. When this latter proportion is about 20.3%, the prophylaxis strategy is a less cost effective strategy (the incremental cost-effectiveness ratio of prophylaxis vs. screening is around 1500 $/LYG). In contrast when this proportion is increased, the prophylaxis strategy becomes more cost-effective. From these data, one may hypothesize that in patients with CD4 count ≤50 cells/μl and a higher cryptococcosis incidence, the

prophylaxis strategy in addition to being a more effective strategy for cryptococcal infection prevention is probably associated with an acceptable cost-effective ratio. In contrast, in patients with CD4 cell count between 51 and 100 cells/μl, prophylaxis strategy is associated with higher cost-effectiveness ratio and screening strategy may be the preferred strategy. One should consider that in addition cryptococcosis systematic screening is clinically valuable for the diagnosis of isolated positive CRAG in serum and asymptomatic cryptococcal meningitis [11,12,13,14]. In the Cambodian study, of the 59 patients with cryptococcal infection, 17 (28.8%) would not have been diagnosed on the day of consultation without the agglutination test performed on serum. These patients received appropriate treatment for asymptomatic isolated positive CRAG or asymptomatic cryptococcal meningitis, which decreased either the risk of developing subsequent cryptococcal meningitis or the risk of mortality. In the absence of treatment these patients may further more develop cryptococcal immune reconstitution inflammatory syndrome [29] that is issue in South East Asia [30].

Results of the present study are based on transition probabilities drawn from real-life data and are applicable to the setting from which the results were derived. They present in addition several limitations and several points should be discussed before they can be used in the field of decision-making. We used a simulation model that combines input data from multiple sources and relies on several assumptions, although most of input data were from Cambodia. We measured resource use and effects of evaluated strategies over a 1-year-period after the time of HIV diagnosis and clinic enrollment (i.e.; the time horizon of the study one year).

However, thanks to cART, HIV disease has now become a long-term chronic disease associated with a life expectancy increasing over time [31]. Long-term cost-effectiveness of cryptococcal infection prevention strategies may be different than results that we have reported in this manuscript. Nevertheless, first we believe that evaluating the cost-effectiveness of cryptococcal infection prevention in the short-term is by itself a valuable information for clinicians and policy makers. Moreover, because morbidities and mortality related to cryptococcal infections primarily occur during the first year following HIV diagnosis, estimating consequences of prevention strategies initiated at HIV care over a 1-year-period allow us to capture important effects related to these strategies. In this analysis, we were not able to estimate the incidence of each specific OI because of lack of available data and thus estimated the incidence of OIs overall. Adverse effects of drugs were not taken into account, and could be an argument in favor of the screening strategy. The exposure of cryptococcosis-free subjects to unnecessary treatment could lead to unnecessary adverse effects including ecological impact and costs. Indeed the primary prophylaxis for cryptococcal infection impact the occurrence of fluconazole resistance on Candida species [32]. Furthermore, fluconazole might have an ecological impact with the emergence of less susceptible Cryptococcus and Candida isolates. This has been well described by Bicanic et al. among symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy [33]. Treatment adherence was assumed to be perfect, which could affect the results of both strategies, as incomplete adherence could affect the efficacy of treatment. Finally, disability weighting associated with years of life lived within categories defined in our model was not available. As such, we expressed our results in cost per year of life gained.

This study suggests that systematic serum CRAG screening and systematic primary prophylaxis strategies in patients with CD4+ count ≤100 cells/µl are very cost-effective strategies for the management of opportunistic cryptococcosis in newly diagnosed HIV-infected patients in Cambodia in 2009, although systematic primary prophylaxis was found to be more effective. Cost-effectiveness ratios associated with these strategies are in line with the cost-effectiveness of other strategies already implemented to prevent OI occurrence in HIV-infected patients in developing countries. Based on the results of this study one may consider that at the enrolment of patients in antiretroviral access program in Cambodia, patients should receive systematic fluconazole prophylaxis when CD4+ count is below 50 cells/µl and rather a systematic serum CRAG screening (for targeted treatment of positive cases) may be considered when CD4+ count is between 51–100 cells/µl.

Supporting Information

Technical Appendix S1
Found at: doi:10.1371/journal.pone.0013856.s001 (0.05 MB DOC)

Author Contributions

Conceived and designed the experiments: RM AT OL SB JPD HC AF YY. Analyzed the data: RM AT OL SB YY. Contributed reagents/materials/analysis tools: RM CQ JPD YM. Wrote the paper: RM AT OL SB CQ JPD HC YM AF YY.

References

1. Scharfstein JA, Paltiel AD, Freedberg KA (1997) The cost-effectiveness of fluconazole prophylaxis against primary systemic fungal infections in AIDS patients. Med Decis Making 17: 373–381.
2. Yazdanpanah Y, Goldie SJ, Paltiel AD, Losina E, Coudeville L, et al. (2003) Prevention of human immunodeficiency virus-related opportunistic infections in France: a cost-effectiveness analysis. Clin Infect Dis 36: 86–96.
3. Freedberg KA, Scharfstein JA, Seage GR, 3rd, Losina E, Weinstein MC, et al. (1998) The cost-effectiveness of preventing AIDS-related opportunistic infections. Jama 279: 130–136.
4. Chariyalertsak S, Sirisanthana T, Saengwonloey O, Nelson KE (2001) Clinical presentation and risk behaviors of patients with acquired immunodeficiency syndrome in Thailand, 1994–1998: regional variation and temporal trends. Clin Infect Dis 32: 955–962.
5. Amornkul PN, Hu DJ, Tansuphasawadikul S, Lee S, Eampokalap B, et al. (2003) Human immunodeficiency virus type 1 subtype and other factors associated with extrapulmonary Cryptococcosis among patients in Thailand with AIDS. AIDS Res Hum Retroviruses 19: 85–90.
6. Jarvis JN, Boulle A, Loyse A, Bicanic T, Rebe K, et al. (2009) High ongoing burden of cryptococcal disease in Africa despite antiretroviral roll out. Aids 23: 1182–1183.
7. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, et al. (2009) Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. Aids 23: 525–530.
8. John L, Nelson M (2004) Primary prophylaxis for cryptococcal meningitis. HIV Med 5: 131–132.
9. Chhin S, Rozycki G, Pugatch D, Harwell JI (2004) Aetiology of meningitis in HIV-infected patients in a referral hospital in Phnom Penh, Cambodia. Int J STD AIDS 15: 48–50.
10. Pichith K, Chanroeun H, Bunna P, Nyvanny N, Thavary S, et al. (2001) [Clinical aspects of AIDS at the Calmette hospital in Phnom Penh, Kingdom of Cambodia A report on 356 patients hospitalized in the Medicine "B" Department of the Calmette Hospital]. Sante 11: 17–23.
11. Micol R, Lortholary O, Sar B, Laureillard D, Ngeth C, et al. (2007) Prevalence, determinants of positivity, and clinical utility of cryptococcal antigenemia in Cambodian HIV-infected patients. J Acquir Immune Defic Syndr 45: 555–559.
12. Jarvis JN, Lawn SD, Vogt M, Bangani N, Wood R, et al. (2009) Screening for cryptococcal antigenemia in patients accessing an antiretroviral treatment program in South Africa. Clin Infect Dis 48: 856–862.
13. Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, et al. (2010) Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clin Infect Dis 51: 448–455.
14. Pongsai P, Atamasirikul K, Sungkanuparph S (2010) The role of serum cryptococcal antigen screening for the early diagnosis of cryptococcosis in HIV-infected patients with different ranges of CD4 cell counts. J Infect 60: 474–477.
15. Liechty CA, Solberg P, Were W, Ekwaru JP, Ransom RL, et al. (2007) Asymptomatic serum cryptococcal antigenemia and early mortality during antiretroviral therapy in rural Uganda. Trop Med Int Health 12: 929–935.
16. Ministry of Health NCfHA, Dermatology and STD (2009) Second Quarterly comprehensive report, 2009 HIV/AIDS & STI Prevention and Care Programme. www.nchads.org/Report/2009%20q2%20en.pdf.
17. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, et al. (2010) Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis 50: 291–322.
18. Lortholary O, Poizat G, Zeller V, Neuville S, Boibieux A, et al. (2006) Long-term outcome of AIDS-associated cryptococcosis in the era of combination antiretroviral therapy. Aids 20: 2183–2191.
19. Goldie SJ, Yazdanpanah Y, Losina E, Weinstein MC, Anglaret X, et al. (2006) Cost-effectiveness of HIV treatment in resource-poor settings–the case of Cote d'Ivoire. N Engl J Med 355: 1141–1153.
20. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, et al. (1997) Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 126: 946–954.
21. Gade W, Hinnefeld SW, Babcock LS, Gilligan P, Kelly W, et al. (1991) Comparison of the PREMIER cryptococcal antigen enzyme immunoassay and the latex agglutination assay for detection of cryptococcal antigens. J Clin Microbiol 29: 1616–1619.
22. Madec Y, Laureillard D, Pinoges L, Fernandez M, Prak N, et al. (2007) Response to highly active antiretroviral therapy among severely immuno-compromised HIV-infected patients in Cambodia. Aids 21: 351–359.

23. Wertheimer AI, Santella TM, Lauver HJ (2004) Successful public/private donation programs: a review of the Diflucan Partnership Program in South Africa. J Int Assoc Physicians AIDS Care (Chic Ill) 3: 74–79, 84–75.
24. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE (2002) A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. Clin Infect Dis 34: 277–284.
25. McCarthy KM, Morgan J, Wannemuehler KA, Mirza SA, Gould SM, et al. (2006) Population-based surveillance for cryptococcosis in an antiretroviral-naive South African province with a high HIV seroprevalence. Aids 20: 2199–2206.
26. World Health Organization. Macroeconomics and health: investing in health for economic development. Report of the commission on macroeconomics and health. [Accessed on what date?]; Available from: http://libdoc.who.int/publications/2001/924154550X.pdf.
27. Yazdanpanah Y, Losina E, Anglaret X, Goldie SJ, Walensky RP, et al. (2005) Clinical impact and cost-effectiveness of co-trimoxazole prophylaxis in patients with HIV/AIDS in Cote d'Ivoire: a trial-based analysis. Aids 19: 1299–1308.
28. Shrestha RK, Mugisha B, Bunnell R, Mermin J, Odeke R, et al. (2007) Cost-utility of tuberculosis prevention among HIV-infected adults in Kampala, Uganda. Int J Tuberc Lung Dis 11: 747–754.
29. Lortholary O, Fontanet A, Memain N, Martin A, Sitbon K, et al. (2005) Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. Aids 19: 1043–1049.
30. Sungkanuparph S, Filler SG, Chetchotisakd P, Pappas PG, Nolen TL, et al. (2009) Cryptococcal immune reconstitution inflammatory syndrome after antiretroviral therapy in AIDS patients with cryptococcal meningitis: a prospective multicenter study. Clin Infect Dis 49: 931–934.
31. Walensky RP, Wolf LL, Wood R, Fofana MO, Freedberg KA, et al. (2009) When to start antiretroviral therapy in resource-limited settings. Ann Intern Med 151: 157–166.
32. Apisarnthanarak A, Mundy LM (2008) The impact of primary prophylaxis for cryptococcosis on fluconazole resistance in Candida species. J Acquir Immune Defic Syndr 47: 644–645.
33. Bicanic T, Harrison T, Niepieklo A, Dyakopu N, Meintjes G (2006) Symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy: the role of fluconazole resistance and immune reconstitution. Clin Infect Dis 43: 1069–1073.