Cost-Effectiveness of Amphotericin B Deoxycholate Versus Itraconazole for Induction Therapy of Talaromycosis in Human Immunodeficiency Virus–Infected Adults in Vietnam

James Buchanan,1,6 James Altunkaya,1 Nguyen Van Kinh,2 Nguyen Van Vinh Chau,3 Vo Trieu Ly,4 Pham Thi Thanh Thuy,5 Vu Hai Vinh,6 Doan Thi Hong Hanh,7 Nguyen Thuy Hang,8 Tran Phuong Thuy,9 Rogier van Doorn,10 Guy Thwaites,11 Alastair Gray,12 and Thuy Le13,14,15

1Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom, 2National Hospital for Tropical Diseases, Hanoi, Vietnam, 3Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam, 4University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam, 5Bach Mai Hospital, Hanoi, Vietnam, 6Viet Nam-Sweden Uong Bi Hospital, Quang Ninh, Vietnam, 7Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam, 8Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam; Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, United Kingdom, and 9Oxford University School of Medicine, Durham, North Carolina, USA

Background. Talaromycosis (penicilliosis) is an invasive fungal infection and a major cause of human immunodeficiency virus (HIV)–related deaths in Southeast Asia. Guidelines recommend induction therapy with amphotericin B deoxycholate; however, treatment with itraconazole has fewer toxic effects, is easier to administer, and is less expensive. Our recent randomized controlled trial in Vietnam found that amphotericin B was superior to itraconazole with respect to 6-month mortality. We undertook an economic evaluation alongside this trial to determine whether the more effective treatment is cost-effective.

Methods. Resource use, direct and indirect costs, and health and quality-of-life outcomes (measured using quality-adjusted life-years [QALYs]) were evaluated for 405 trial participants from 2012 to 2016. Both a Vietnamese health service and a broader societal costing perspective were considered. Mean costs and QALYs were combined to calculate the within-trial cost-effectiveness of amphotericin vs itraconazole from both perspectives.

Results. From a Vietnamese health service perspective, amphotericin increases costs but improves health outcomes compared to itraconazole, at a cost of $3013/QALY gained. The probability that amphotericin is cost-effective at a conventional (World Health Organization CHOICE) threshold of value for money is 46%. From a societal perspective, amphotericin is cost-reducing and improves outcomes compared to itraconazole, and is likely to be a cost-effective strategy at any value for money threshold greater than $0.

Conclusions. Our analysis indicates that induction therapy with amphotericin is a cost-effective treatment strategy for HIV-infected adults diagnosed with talaromycosis in Vietnam. These results provide the evidence base for health care providers and policy makers to improve access to and use of amphotericin.

Keywords. amphotericin B; cost-effectiveness; HIV; itraconazole; talaromycosis.

Talaromycosis (formerly penicilliosis) is an invasive fungal infection caused by the thermally dimorphic fungus Talaromyces marneffei that is endemic throughout Southeast Asia, southern China, and northeastern India. Patients with advanced human immunodeficiency virus (HIV) disease (CD4 count <100 cells/mm³) are at risk and develop disseminated infection involving the skin, lung, liver, spleen, lymphatics, bloodstream, and bone marrow [1]. Driven by the HIV pandemic, talaromycosis is now the third most common cause of HIV-related infections; it accounts for up to 25% of HIV-related hospital admissions and is a leading cause of HIV-associated bloodstream infections and death in Vietnam and southern China [2–10]. Increasingly, talaromycosis is being diagnosed in patients with immunodeficiency conditions other than HIV (including patients with interferon-γ autoantibody, autoimmune diseases, cancers, and after undergoing organ and bone marrow transplantation) [11]. Talaromycosis is also increasingly diagnosed in immigrants and in returning travelers from Southeast Asia [12]. The mortality rate on antifungal therapy is 10%–30% in HIV-infected patents [2, 3, 6–8], and 50% in non-HIV-infected patients [11].

Current treatment options in endemic regions are largely limited to 2 drugs, amphotericin B deoxycholate (hereafter, “amphotericin”) and itraconazole. Prior to the trial that underpins the economic evaluation reported in this article, international guidelines recommended induction therapy with amphotericin, delivered intravenously at a daily dose of 0.7–1 mg/kg of body
weight for 2 weeks, followed by consolidation therapy with itraconazole, delivered orally at a dose of 400 mg per day for 10 weeks [13, 14]. This recommendation was informed by expert opinion and the results of a noncomparative study using this strategy in Thailand. However, in low-resource countries such as Vietnam, Myanmar, and India, itraconazole is used more frequently than amphotericin because it is widely available in oral formulation, is cheaper, and has fewer side effects.

We recently completed a randomized controlled trial comparing itraconazole vs amphotericin for induction therapy of talaromycosis in 5 hospitals in Vietnam (Itraconazole versus Amphotericin B for Penicilliosis [IVAP] trial) [15]. We found amphotericin to be superior with respect to 6-month mortality (11.3% vs 21.0% in the itraconazole group; absolute risk difference, 9.7% [95% confidence interval [CI], 2.8%–16.6%]). Amphotericin treatment was also associated with faster clearance of fungemia, faster resolution of symptoms, and lower rates of relapse and immune reconstitution inflammatory syndrome. Although more frequent drug-related adverse events were observed in the amphotericin group, the overall incidence of serious adverse events was lower.

As amphotericin is more expensive than itraconazole, the IVAP trial findings have significant implications for limited health care budgets in HIV-endemic countries in Southeast Asia. However, there are no data on whether the more effective treatment is cost-effective. We undertook an economic evaluation alongside the IVAP trial to evaluate resource use, costs, and health outcomes associated with the 2 treatments, and combine these data in a cost-effectiveness analysis to inform treatment policy for talaromycosis.

**METHODS**

Here we describe our analytical approach; how data were collected on costs, resource use, and outcomes for each treatment strategy; how missing data were addressed; and the analyses performed.

**Analytical Approach**

A modified intention-to-treat approach was adopted for the economic evaluation, as per the IVAP trial. Thirteen of 440 patients initially randomized to treatment were excluded because they did not receive the study drug, or there was no microbiological evidence of talaromycosis. Twenty-two patients were excluded because their hospital bills were missing; the majority (14) were from 1 of 5 study sites. In total, 405 patients were included in this analysis (Figure 1).

The economic evaluation followed the time frame of the trial, with resource use, costs, and health and quality-of-life (QoL) outcomes evaluated for each patient from hospital admission until discharge (“inpatient period”), then until the end of 6-month follow-up (“follow-up period”). The economic evaluation results were calculated from the perspective of the

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**Figure 1.** Summary of patients included in the economic evaluation.
The societal analysis included the following costs (details in Non–Health Care Resource Use and Costs).

Resource Use and Costs

Health Care Resource Use and Costs.
Data on health care resource use were prospectively collected at study enrollment, end of the inpatient period, and end of follow-up. Data were collected on all laboratory and radiographic investigations, adverse events, inpatient stays, outpatient visits, treatments and interventions including blood and platelet transfusion, and emergency care. Costs were extracted from patient billing records, as no standard unit costs for Vietnamese health care were available.

Use of itraconazole and amphotericin during the inpatient period was recorded within the trial. In the itraconazole arm, patients received a loading dose of 600 mg per day for 3 days, then 400 mg per day thereafter. In the amphotericin arm, patients received 0.7 mg per kg per day. During follow-up, all patients received a consolidation dose of 400 mg itraconazole per day for 10 weeks, then 200 mg per day thereafter.

The costs associated with itraconazole and amphotericin treatment were covered by trial funding. For this analysis, we used unit costs reflecting local market prices: 18 500 Vietnamese Dong (VND) (US$0.89) per 100-mg tablet for itraconazole and 416 920 VND (US$20) per 50-mg vial of amphotericin. As the price for amphotericin was originally expressed in US dollars, we converted this into VND using the exchange rate on the date of the first hospital admission in the trial (20 846 VND to US$1) [16], to reflect local market prices at the point of drug purchase. If an entire vial was not required, the excess was discarded.

Non–Health Care Resource Use and Costs.
The societal analysis included the following costs (details in Supplementary Materials Part 1):

- **Patient lost income**: Data were collected on income lost during the inpatient period and days off work during the follow-up period, but no data were collected on income lost during the follow-up period. If patients provided data on income lost during the inpatient period, their daily wage rate was applied to time off work during the follow-up period; otherwise, daily wage rates by region were applied to time off work [17].
- **Carer lost income**: Data were collected on income lost by carers attending patients during the inpatient and follow-up periods.
- **Childcare costs**: Data were collected on days of childcare required during the inpatient and follow-up periods.
- **Patient out-of-pocket spending**: Data were collected on patient out-of-pocket spending during the inpatient and follow-up periods. This included spending on over-the-counter medications, user fees, food and drink (while hospitalized), and medical supplies.
- **Patient travel costs**: Data were collected on travel costs to and from hospital during the inpatient and follow-up periods.

Health and Quality-of-Life Outcomes

All-cause mortality was recorded throughout the trial. Patients completed EQ-5D-5L health status surveys on admission (survey 1), after the 2-week inpatient period (survey 2), and at 24-week follow-up (survey 3) (Supplementary Materials Part 1). Each completed EQ-5D-5L survey yielded a health-related QoL profile, which was assigned an index value (“utility”). A recent EQ-5D-5L valuation study for Vietnam was used to calculate index values [19, 20]. Utility was set to zero from the date of death onward. Linear interpolation was used to calculate quality-adjusted survival between the dates of the 3 surveys and/or death, expressed as a fraction of 1 year in full health (quality-adjusted life-years [QALYs]). Differences in QoL between treatment arms at baseline were adjusted for observed QoL in our base-case analysis [21].

Missing Data

The overall level of missing data was low (described in Supplementary Materials Part 2). Multiple imputation with chained equations was used to replace missing observations with predicted values based on observed data [22], using Stata version 14 software (StataCorp, College Station, Texas).

Analyses Performed

Main Analysis.
Cost data were summarized by costing perspective (health care provider, societal) and study period (inpatient, follow-up) (Figure 2). Within-trial costs and QALYs were not discounted due to the short time horizon of the study, as no patient had a combined inpatient and follow-up period that exceeded 1 year. Mean costs and QALYs accrued in each study arm were calculated and combined in an incremental analysis to calculate the cost-effectiveness of amphotericin vs itraconazole from both costing perspectives. Results are presented in 2016 international dollars, converted from Vietnamese Dong using the 2016 World Bank gross domestic product (GDP) purchasing power parity conversion factor for Vietnam (7315.61 VND per international dollar) [23]. We also calculated cost-effectiveness using life-years as the outcome measure (Supplementary Materials Part 7).
Uncertainty surrounding the results was evaluated using nonparametric bootstrapping. For each of the 75 imputed datasets, 1000 bootstrap resamples were drawn. The resulting cost and effect pairs were used to calculate cost-effectiveness acceptability curves that evaluated which treatment was the cost-effective strategy at a range of cost-effectiveness thresholds. The CIs for incremental cost-effectiveness ratios were calculated using the percentile approach. Assessing value for money requires a cost-effectiveness threshold, but consensus on the appropriate threshold for Vietnam is absent. We use the World Health Organization Choosing Interventions That Are Cost-Effective (WHO-CHOICE) threshold for very good value for money of annual GDP per capita in Vietnam, which in 2016 was $2171 [24, 25]. In a sensitivity analysis we also consider low and high cost-effectiveness thresholds as proposed by Woods et al [26], using an opportunity cost approach, of $144 and $982, respectively.

**Sensitivity Analyses.**
Sensitivity analyses explored the impact on our results if drug costs were 50% above or below their assumed level.

**Lifetime Analysis.**
The within-trial analysis ignores cost or outcome differences continuing beyond the trial follow-up period. To address this, we conducted a lifetime analysis that estimated costs and health outcomes accrued by patients after trial follow-up had ceased. Costs and health outcomes were then discounted to present values at a rate of 3% per annum and combined with

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**Figure 2.** Summary of cost components by study period and costing perspective.
the within-trial results to derive lifetime estimates (details are shown in Supplementary Materials Part 3).

RESULTS

Patient characteristics are described in Supplementary Materials Part 4. Baseline differences by study arm in mean age (34 years), sex (68% male), proportion of patients who were intravenous drug users (31%), and QoL were not statistically significant.

Resource Use and Costs

There were few significant differences in resource use by study arm across the inpatient and follow-up periods (Supplementary Materials Part 5). Healthcare–related resource use was higher for patients in the itraconazole arm during the follow-up period; however, the differences were not statistically significant.

Tables 1–3 present the cost results (see Supplementary Materials Part 6 for results in VND). From a health care provider perspective, patients in the amphotericin arm had significantly higher costs during the inpatient period (mean difference, $586 [95% CI, $239–$933]), primarily due to higher drug costs, but significantly lower costs during the follow-up period (mean difference, –$504 [95% CI, –$924 to –$84]), primarily due to fewer subsequent hospitalizations and outpatient clinic visits. Over the entire trial, patients in the amphotericin arm had slightly but not significantly higher costs from a health care provider perspective (mean difference, $82 [95% CI, –$501 to $666]) (Table 1).

Non–health care costs were slightly but not significantly lower among patients in the amphotericin arm, during both the inpatient and follow-up periods, with a nonsignificant mean difference over the entire trial of –$155 (95% CI, –$498 to $188) (Table 2).

Combining health care and non–health care costs in a societal perspective (Table 3), patients in the amphotericin arm had significantly higher costs during the inpatient period (mean difference, $515 [95% CI, $49–$980]), but significantly lower costs during the follow-up period (mean difference, –$587 [95% CI, –$1104 to –$71]). Over the entire trial the mean difference was –$73 (95% CI, –$831 to $686).

Health and QoL Outcomes.

Patients in the amphotericin arm generally reported better QoL at both discharge and end of follow-up (Supplementary Table 7.1). Mean utility scores were significantly higher for amphotericin than for itraconazole at all 3 study timepoints (Figure 3). Adjusted for small differences in baseline QoL, patients in the amphotericin arm had significantly higher quality-adjusted survival (mean QALY difference, 0.027 [95% CI, .002–.052]; Supplementary Table 7.2). Patients in the amphotericin arm also gained significantly more life-years (mean difference, 0.016 life-years [95% CI, .001–.031]; Supplementary Materials Part 7).

Cost-Effectiveness Analysis.

From a health care provider perspective, amphotericin improves health outcomes compared to itraconazole at a cost of $3013 per QALY gained (Table 4). When judged against the WHO-CHOICE cost-effectiveness threshold of $2171, and when taking into account uncertainty surrounding these results

Table 1. Mean Patient Costs From a Healthcare Provider Perspective, in 2016 International Dollars

| Study Timepoint | Cost Category          | Study Arm: Mean (SE) ($) | Difference*, Mean (95% CI) ($) |
|-----------------|------------------------|--------------------------|-------------------------------|
| Inpatient period (n = 405) | Diagnosis              | Amphotericin B 432 (16)  Itraconazole 428 (16) | 4 (–40 to 48) |
|                  | Inpatient stays        | 183 (14) 171 (8)         | 12 (–20 to 45) |
|                  | Drugs                  | 843 (83) 872 (88)        | –30 (–267 to 208) |
|                  | Procedures and operations | 12 (4) 10 (2)  | 2 (–6 to 10) |
|                  | Blood transfusions     | 227 (23) 177 (23)        | 51 (–13 to 114) |
|                  | Platelets              | 53 (19) 79 (28)          | –26 (–92 to 40) |
|                  | Other costs            | 105 (7) 90 (7)           | 15 (–4 to 35) |
|                  | Trial drugs            | 737 (16) 180 (9)         | 557 (520–594)b |
|                  | Total—inpatient period | 2592 (126) 2066 (124)    | 586 (239–933)b |
| Follow-up period (n = 379) | Trial drugs            | 1048 (22) 1006 (24)      | 42 (–23 to 106) |
|                  | Hospital costs         | 361 (82) 895 (195)       | –534 (–952 to –117)b |
|                  | Other test costs       | 1 (0) 3 (1)              | –2 (–4 to –1)b |
|                  | Other diagnostic costs | 50 (2) 59 (3)            | –9 (–16 to –1)b |
|                  | Total—follow-up period | 1459 (85) 1963 (195)     | –504 (–924 to –841)b |
|                  | Total—inpatient and follow-up period | 4052 (164) 3969 (247) | 82 (–501 to 666) |

Abbreviations: CI, confidence interval; SE, standard error.

*aDifference = amphotericin minus itraconazole.
bSignificant at 1% level.
cSignificant at 5% level.
(Supplementary Figures 8.1 and 8.2), there is a 46% probability that amphotericin is the cost-effective strategy. When a societal perspective is considered, amphotericin reduces costs and improves health outcomes, with a 63% probability of being cost-effective. When life-years were used as the outcome measure, the cost per life-year gained for amphotericin vs itraconazole was $5079 from a health care provider perspective (Supplementary Materials Part 7).

Sensitivity and Lifetime Analyses.

When the amphotericin cost is reduced by 50%, the probability that amphotericin is the cost-effective treatment strategy increases from 46% to 87% (health care provider perspective) and from 63% to 90% (societal perspective). Changes in the cost of itraconazole have a smaller impact on the cost-effectiveness analysis results (Supplementary Materials Part 9).

The probability that amphotericin is cost-effective from a health system perspective using the Woods et al cost-effectiveness threshold is 39% at the lower threshold and 42% at the higher threshold (Supplementary Materials Parts 8 and 9). From a societal perspective, the probability that amphotericin is the cost-effective treatment strategy is 58% at the lower and 60% at the higher Woods threshold.

When the trial results are extended to a lifetime perspective (Supplementary Materials Part 3), amphotericin increases costs (mean difference, $725 [95% CI, $458–$996]) and improves health outcomes (mean QALY difference, 1.06). The discounted lifetime cost-effectiveness from a societal perspective is $655/QALY gained, below the WHO cost-effectiveness threshold ($2171).

DISCUSSION

In this randomized trial-based economic evaluation of the use of amphotericin vs itraconazole for induction therapy of HIV-associated talaromycosis in Vietnam, we found that, from a health care perspective, amphotericin increases costs and improves health outcomes compared to itraconazole. The probability that amphotericin is the cost-effective treatment strategy at the WHO-CHOICE cost-effectiveness threshold is 46%. However, viewed from a societal perspective that includes broader costs to patients and society, amphotericin is cost-saving and improves outcomes compared to itraconazole, and is therefore likely to be a cost-effective strategy at any threshold greater than $0. The higher costs of amphotericin during the inpatient period are offset by lower health care costs and reduced

| Study Timepoint | Cost Category                  | Study Arm: Mean (SE) ($) | Differencea, Mean (95% CI) ($) |
|-----------------|--------------------------------|--------------------------|--------------------------------|
| Inpatient period (n = 405) | Patient out-of-pocket costs | 450 (36) | 477 (42) | −27 (−135 to 130) |
|                  | Patient travel costs           | 97 (11)    | 114 (15)   | −17 (−55 to 20)    |
|                  | Patient lost income            | 273 (37)   | 299 (50)   | −26 (−148 to 96)   |
|                  | Carer lost income              | 196 (22)   | 202 (20)   | −6 (−45 to 52)     |
|                  | Childcare costs                | 79 (9)     | 74 (10)    | 5 (−21 to 31)      |
| Total—inpatient period | Patient out-of-pocket costs | 1095 (69) | 1166 (87)  | −71 (−289 to 146)  |
| Follow-up period (n = 379) | Patient travel costs           | 228 (50)   | 210 (37)   | 19 (−104 to 138)   |
|                  | Patient lost income            | 193 (24)   | 187 (21)   | 6 (−57 to 69)      |
|                  | Carer lost income              | 134 (24)   | 198 (56)   | −64 (−183 to 55)   |
|                  | Childcare costs                | 82 (24)    | 102 (25)   | −20 (−89 to 49)    |
| Total—follow-up period | Total—inpatient and follow-up period | 682 (73)   | 765 (94)   | −84 (−316 to 148)  |

Abbreviations: CI, confidence interval; SE, standard error.

Table 3. Mean Societal (Healthcare Provider and Non–Health Care) Costs per Patient, in 2016 International Dollars

| Cost Category                        | Study Arm: Mean (SE) ($) | Differencea, Mean (95% CI) ($) |
|--------------------------------------|--------------------------|--------------------------------|
| Inpatient period                      | Amphotericin B           | 3688 (156)                     | 3173 (178) | 515 (49–980)b               |
| Follow-up period                      | Amphotericin B           | 2141 (129)                     | 2729 (230) | −587 (−1104 to −71)b         |
| Total—inpatient and follow-up period | Amphotericin B           | 5829 (225)                     | 5901 (316) | −73 (−831 to 686)            |

Abbreviations: CI, confidence interval; SE, standard error.

Table 2. Mean Non–Health Care Costs, in 2016 International Dollars

| Cost Category                        | Study Arm: Mean (SE) ($) | Differencea, Mean (95% CI) ($) |
|--------------------------------------|--------------------------|--------------------------------|
| Patient out-of-pocket costs          | Amphotericin B           | 450 (36)                       | 477 (42) | −27 (−135 to 130) |
| Patient travel costs                 | Amphotericin B           | 97 (11)                        | 114 (15) | −17 (−55 to 20) |
| Patient lost income                  | Amphotericin B           | 273 (37)                       | 299 (50) | −26 (−148 to 96) |
| Carer lost income                    | Amphotericin B           | 196 (22)                       | 202 (20) | −6 (−45 to 52) |
| Childcare costs                      | Amphotericin B           | 79 (9)                         | 74 (10)  | 5 (−21 to 31)  |
| Total—inpatient period               | Amphotericin B           | 1095 (69)                      | 1166 (87) | −71 (−289 to 146) |

Abbreviations: CI, confidence interval; SE, standard error.

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| Childcare costs                      | Amphotericin B           | 79 (9)                         | 74 (10)  | 5 (−21 to 31)  |
| Total—inpatient period               | Amphotericin B           | 1095 (69)                      | 1166 (87) | −71 (−289 to 146) |

Abbreviations: CI, confidence interval; SE, standard error.

aDifference = amphotericin minus itraconazole.
lost income during the follow-up period, driven by lower incidence of disease complications.

Our results complement the main findings of the clinical trial, which found that amphotericin therapy was associated with reduced mortality, faster resolution of symptoms, and lower rates of disease complications. This analysis provides reliable evidence that induction therapy with amphotericin is likely to be a cost-effective treatment strategy for HIV-infected adults diagnosed with talaromycosis in countries with similar health care and economic settings in Southeast Asia. This conclusion is greatly strengthened when taking into account broader societal cost savings, the longer-term benefits of this therapy, and trends in reductions in the cost of amphotericin and duration of treatment since our study was conducted. In particular, the statistically significant survival benefit reported in the main trial results translates in our extrapolation into a substantial difference in life expectancy and hence a much lower lifetime cost-effectiveness ratio.

The cost-effectiveness of amphotericin induction therapy can be compared with that of other interventions considered cost-effective in Vietnam and Southeast Asia to reduce HIV-related morbidity and mortality, while bearing in mind differences in study methods, dates, perspectives, and settings: for example, HIV prevention programs in Vietnam ($2344 per death averted) [27]; methadone maintenance treatment to prevent HIV acquisition among injection drug users in Vietnam ($1964 per QALY gained) [28]; screening HIV-infected adults in Vietnam for cryptococcal infection using an antigen test ($119–$190 per life-year gained) [29]; strategies for cryptococcosis prevention in HIV-infected patients in Cambodia

Table 4. Cost-Effectiveness Analysis Results for Amphotericin Versus Itraconazole, in 2016 International Dollars

| Costing Perspective | Incremental Costs, $ | Incremental QALYs | Cost per QALY Gained, $ | 95% CI for Cost-Effectiveness Ratio, $ | Probability of Amphotericin Being Cost-Effective at WHO-CHOICE Per-Capita Income Threshold ($2171), % |
|----------------------|----------------------|-------------------|------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------|
| Healthcare provider costs only | 82                    | 0.027             | 3013                   | Cost saving to 51 913 per QALY gained | 46                                                                                               |
| Societal costs       | –73                   | 0.027             | NA*                   | Cost saving to 51 960 per QALY gained | 63                                                                                               |
| Healthcare provider costs only | 82                    | 0.034             | 2438                   | Cost saving to 41 999 per QALY gained | 48                                                                                               |
| Societal costs       | –73                   | 0.034             | NA*                   | Cost saving to 38 110 per QALY gained | 65                                                                                               |

Incremental figures = amphotericin minus itraconazole.
Abbreviations: CI, confidence interval; NA, not applicable; QALY, quality-adjusted life-year; WHO-CHOICE, World Health Organization Choosing Interventions That Are Cost-Effective.

*Amphotericin reduces costs and improves health outcomes.
includes some future lifetime medical costs in later years of life. Although we show that amphotericin is likely to be a cost-effective treatment strategy, it is currently not widely available in Southeast Asia, has higher upfront drug costs, and requires higher levels of knowledge and skills in drug administration, and monitoring and management of side effects. Widespread adoption would require the health sector to preallocate financial resources to drug procurement and training of health care staff in drug administration and monitoring, which requires careful budget impact analyses. Implementation would be challenging, particularly in district- and commune-level hospitals where the volume of talaromycosis patients is lower and nursing skills and facilities for intravenous infusion and monitoring are limited. Whether current guidelines on induction therapy in talaromycosis are actually followed will also affect the affordability of changing health care practice.

Our study has several strengths. We used detailed data on costs and morbidity and mortality outcomes carefully collected within a randomized controlled trial, minimizing unobserved bias and reducing the number of assumptions required. Data on costs incurred by patients and carers outside the health sector were included, permitting a societal analytical perspective. QoL data were collected directly from patients, not derived from previous studies, and we were able to use locally estimated utility values. We also fully considered patient- and parameter-level uncertainty, and undertook an illustrative extrapolation of the cost-effectiveness estimates beyond the timeframe of the clinical study. Finally, IV AP was a pragmatic trial conducted in 5 central and provincial hospitals; hence, the clinical and cost-effectiveness results are potentially generalizable across Vietnam and similar health care settings in the wider region. While no standard national unit costs for Vietnamese health care were available, comprehensive billing records were available to generate accurate costs for our patient sample. Our results are less generalizable to higher-resource countries such as Singapore or Thailand, where access to antiretroviral therapy and health care financing systems and costs are substantially different.

Our study also has some limitations. First, because we quantified health outcomes using QALYs, comparisons with studies that use disability-adjusted life-years (DALYs)—a common metric in economic evaluations in developing countries—are more difficult [32]. However, a recent study concluded that the choice of approach to compute health benefits seldom alters the conclusions of such studies. The authors further noted that any uncertainty arising from using either QALYs or DALYs is unlikely to be greater than that due to other study variables, such as the variations in drug cost considered in our analysis [33]. A further recent study supports this conclusion [34]. Second, our lifetime analysis was relatively simple and excludes some future lifetime medical costs in later years of life. However, the main variable driving these long-term estimates was differences in the numbers of patients alive in each trial arm at end of follow-up, a strong position from which to assume some continuing benefit. Third, we acknowledge that costs generated from billing records may not fully generalize to reflect national health care opportunity costs. However, in the absence of standard unit costs for Vietnamese health care resources, our costing approach gives the best available approximation. We further acknowledge that the economic perspective may vary between rural and urban patients; however, we did not collect reliable data to compare these perspectives. Fourth, although the overall level of missing data was low, we acknowledge that alternative analytical choices to implement the multiple imputation of missing data within a bootstrapped analysis may affect the magnitude of decision uncertainty [35]. Finally, although the trial protocol stipulated that all patients must remain in hospital for the 14-day duration of induction therapy, some patients in the itraconazole arm might in practice have been judged well enough for early discharge on oral itraconazole therapy. Inpatient costs accrued by patients in the itraconazole arm could therefore be overestimated.

In conclusion, our study provides new trial-based evidence that induction therapy using amphotericin is likely to be a cost-effective treatment strategy for HIV-infected adults diagnosed with talaromycosis in Vietnam and similar settings in Southeast Asia. Although the alternative treatment—itraconazole—is cheaper, amphotericin leads to lower health care costs and reduced income losses, and is associated with improved quality and quantity of life. Our findings support current treatment guidelines and augment the evidence base for the health care sector to invest in improving access to current and new formulations of amphotericin for HIV patients diagnosed with talaromycosis across Southeast Asia.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Patient consent statement. Written informed consent was obtained from all the patients or their representatives. The protocol was approved by the independent ethics committee at each participating hospital, by the Vietnam Ministry of Health, and by the Oxford University Tropical Research Ethics Committee. The Vietnam Ministry of Health and an independent data monitoring and ethics committee oversaw the safety of the trial.

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References

1. Limper AH, Adenis A, Le T, Harrison TS. Fungal infections in HIV/AIDS. Lancet Infect Dis 2017; 17:e334–43.
2. Larsson M, Nguyen LH, Wertherme HF, et al. Clinical characteristics and outcome of Penicillium marneffei infection among HIV-infected patients in northern Vietnam. AIDS Res Ther 2012; 9:24.
3. Le T, Wolbers M, Chi NH, et al. Epidemiology, seasonality, and predictors of outcome of AIDS-associated Penicillium marneffei infection in Ho Chi Minh City, Viet Nam. Clin Infect Dis 2011; 52:945–52.
4. Vu Hai V, Ngo AT, Ngo VH, et al. Penicilliosis in Vietnam: a series of 94 patients [in French]. Rev Med Interne 2010; 31:812–8.
5. Nga TV, Parry CM, Le T, et al. The decline of typhoid and the rise of non-typhoid salmonellosis and fungal infections in a changing HIV landscape: bloodstream infection trends over 15 years in southern Vietnam. Trans R Soc Trop Med Hyg 2012; 106:26–34.
6. Hu XY, Zhang JM, Li XQ, et al. Penicillium marneffei infection: an emerging disease in mainland China. Mycopathologia 2013; 175:57–67.
7. Son VT, Khue PM, Strobel M. Penicilliosis and AIDS in HaiPhong, Vietnam: evolution and predictive factors of death. Med Mal Infect 2014; 44:495–501.
8. Jiang J, Meng S, Huang S, et al. Effects of Talaromyces marneffei infection on mortality of HIV/AIDS patients in southern China: a retrospective cohort study. Clin Microbiol Infect 2019; 25:233–41.
9. Qi T, Zhang R, Shen Y, et al. Etiology and clinical features of 229 cases of bloodstream infection among Chinese HIV/AIDS patients: a retrospective cross-sectional study. Eur J Clin Microbiol Infect Dis 2016; 35:1767–70.
10. Ranjana KH, Priyokumar K, Singh TJ, et al. Disseminated Penicillium marneffei infection among HIV-infected patients in Manipur state, India. J Infect 2002; 45:268–71.
11. Chan JPW, Lau SKP, Yuen KY, Woo PCY. Talaromyces (Penicillium) marneffei infection in non-HIV-infected patients. Emerg Microbes Infect 2016; 5:e19.
12. Antinori S, Giannelli E, Bonaccurso C, et al. Disseminated Penicillium marneffei infection in an HIV-positive Italian patient and a review of cases reported outside endemic regions. J Travel Med 2006; 13:181–8.
13. Edwards S, Dockrell DH, Nelson M. Special issue: British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011 introduction. HIV Med 2011; 12:6–7.
14. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009; 58(RR-4):1–207.
15. Le T, Kinh NV, Cuc NTK, et al. IVAP Investigators. A trial of itraconazole or amphotericin B for HIV-associated talaromycosis. N Engl J Med 2017; 376:2329–40.
16. Currency Table: VND — Vietnamese Dong. Available at: http://www.xe.com/currencytables/?from=VND&date=2012-10-09. Accessed 02 May 2017.
17. General Statistics Office of Vietnam. Available at: https://www.gso.gov.vn/en/pxweb/?psid=E1127&theme=Health%2C%20Culture%2C%20Sport%20and%20Living%20standard. Accessed 18 July 2021.
18. WageIndicator. Minimum wage—Vietnam. https://wageindicator.org/salary/minimum-wage/vietnam. Accessed 2 May 2017.
19. Mai VQ, Sun S, Minh HV, et al. An EQ-5D-3L value set for Vietnam. Qual Life Res 2020; 29:1923–33.
20. EuroQol EQ-5D-3L Value Sets. Available at: https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/valuation-standard-value-sets/. Accessed 18 July 2021.
21. Manca A, Hawkins N, Sculptor MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ 2005; 14:487–96.
22. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. Pharmacoeconomics 2014; 32:1157–70.
23. World Bank. PPP conversion factor, GDP (LCU per international $)—Vietnam. https://data.worldbank.org/indicator/PA.NUS.PPPLOCATIONS?V. Accessed 29 April 2021.
24. Bertram MY, Lauer JA, De Joncheere E, et al. Cost-effectiveness thresholds: pros and cons. Bull World Health Organ 2016; 94:925–30.
25. United Nations Data. A world of information. http://data.un.org/. Accessed 02 May 2017.
26. Woods B, Revill P, Sculptor M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. Value Health 2016; 19:929–35.
27. Pham QD, Wilson DP, Kerr CC, et al. Estimating the cost-effectiveness of HIV prevention programmes in Vietnam, 2006–2010: a modelling study. PLoS One 2015; 10:e0133171.
28. Tran BX, Ohinmaa A, Duong AT, et al. The cost-effectiveness and budget impact of Vietnam’s methadone maintenance treatment programme in HIV prevention and treatment among injection drug users. Glob Public Health 2012; 7:1080–94.
29. Smith RM, Nguyen TA, Ha HT, et al. Prevalence of cryptococcal antigenemia and cost-effectiveness of a cryptococcal antigen screening program—Vietnam. PLoS One 2013; 8:e62213.
30. Micol R, Tahajamady A, Lorpholay O, et al. Cost-effectiveness of primary prophylaxis of AIDS-associated cryptococcosis in Cambodia. PLoS One 2010; 5:e13856.
31. Pho MT, Swaminathan S, Kumarasamy N, et al. The cost-effectiveness of tuberculosis preventive therapy for HIV-infected individuals in southern India: a trial-based analysis. PLoS One 2012; 7:e63001.
32. World Health Organization. Metrics: disability-adjusted life year (DALY). http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/. Accessed 10 April 2018.
33. Augustovski F, Colantonio LD, Galante J, et al. Measuring the benefits of health-care: DALY’s and QALY’s—does the choice of measure matter? a case study of two preventive interventions. Int J Health Policy Manag 2018; 7:120–36.
34. Feng X, Kim DD, Cohen JT, et al. Using QALYs versus DALYs to measure cost-effectiveness: how much does it matter? Int J Technol Assess Health Care 2020; 36:96–103.
35. Brand J, van Buuren S, le Cessie S, van den Hout W. Combining multiple imputation and bootstrap in the analysis of cost-effectiveness trial data. Stat Med 2019; 38:210–20.