Comparison of the Early Fungicidal Activity of High-Dose Fluconazole, Voriconazole, and Flucytosine as Second-Line Drugs Given in Combination With Amphotericin B for the Treatment of HIV-Associated Cryptococcal Meningitis

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(See the Editorial Commentary by Bennett, on pages 129–30.)

Background. HIV-associated cryptococcal meningitis is associated with an estimated 600 000 deaths worldwide per year. Current standard initial therapy consists of amphotericin B (AmB) plus flucytosine (5-FC), but 5-FC remains largely unavailable in Asia and Africa. Alternative, more widely available, and/or more effective antifungal combination treatment regimens are urgently needed.

Methods. Eighty HIV-seropositive, antiretroviral naive patients presenting with cryptococcal meningitis were randomized to 4 treatment arms of 2 weeks duration: group 1, AmB (0.7–1 mg/kg) and 5-FC (25 mg/kg 4 times daily); group 2, AmB (0.7–1 mg/kg) and fluconazole (800 mg daily); group 3, AmB (0.7–1 mg/kg) and fluconazole (600 mg twice daily); and group 4, AmB (0.7–1 mg/kg) and voriconazole (300 mg twice daily). The primary end point was the rate of clearance of infection from the cerebrospinal fluid (CSF) or early fungicidal activity (EFA), as determined by results of serial, quantitative CSF cryptococcal cultures.

Results. There were no statistically significant differences in the rate of clearance of cryptococcal colony-forming units (CFU) in CSF samples among the 4 treatment groups; the mean (± standard deviation) EFA for treatment groups 1, 2, 3, and 4 were −0.41 ± 0.22 log CFU/mL CSF/day, −0.38 ± 0.18 log CFU/mL CSF/day, −0.41 ± 0.35 log CFU/mL CSF/day, and −0.44 ± 0.20 log CFU/mL CSF/day, respectively. Overall mortality was 12% (9 of 78 patients died) at 2 weeks and 29% (22 of 75 patients died) at 10 weeks, with no statistically significant differences among groups. There were few laboratory abnormalities related to the second agents given; in particular, there were no statistically significant (≥grade 3) increases in alanine transaminase level or decreases in neutrophil count.

Conclusions. There was no statistically significant difference in EFA between AmB in combination with fluconazole and AmB plus 5-FC for the treatment of HIV-associated cryptococcal meningitis. AmB plus fluconazole (800–1200 mg/day) represents an immediately implementable alternative to AmB plus 5-FC. AmB plus voriconazole is an effective alternative combination in patients not receiving interacting medications.
There are an estimated 900,000 cases of cryptococcal meningitis (CM) worldwide per year [1]. The highest burden is in sub-Saharan Africa, where it is the most common cause of adult meningitis in many areas [2–5], with an estimated 720,000 cases and 500,000 deaths per year [1]. This is in keeping with prospective mortality data that suggest that 10%–20% of all deaths among HIV-infected patients in Africa are attributable to cryptococcal infection [6–8].

Current recommended therapy for CM consists of 2 weeks of amphotericin B (AmB) in combination with fluconazole (5-FC) [9]. However, 5-FC is currently not available in most developing countries in Asia and Africa, where CM is most prevalent. This is in contrast to fluconazole, which is widely available, in generic formulation or through a donation program [10]. Voriconazole is a relatively new broad-spectrum triazole with excellent in vitro and in vivo activity against Cryptococcus neoformans and good cerebrospinal fluid (CSF) penetration [11–14]. Voriconazole has yet to be evaluated in comparative studies for the treatment of CM.

Therefore, the primary objective of this study was to compare the rate of clearance of infection from the CSF (early fungicidal activity [EFA]) of 3 AmB-containing antifungal regimens (AmB + fluconazole [800 mg daily], AmB + fluconazole [600 mg twice daily], and AmB + voriconazole [300 mg twice daily]) with the EFA of AmB and 5-FC and to examine the safety of these regimens. EFA is associated with 2- and 10-week clinical outcome [15] and provides a means to compare the antifungal activity of alternate regimens in small phase II studies [16].

**MATERIALS AND METHODS**

**Participants**

From August 2006 through October 2008, 21 study patients were recruited at GF Jooste Hospital in Cape Town, Western Cape, South Africa, and 69 patients at Edendale Hospital in Pietermaritzburg, KwaZulu-Natal, South Africa. The study was approved by the Research Ethics Committees of the University of Cape Town, the University of KwaZulu-Natal, Edendale Hospital, St George’s Hospital (London), the KwaZulu-Natal Department of Health, and the Medicines Control Council of South Africa. The trial was registered (ISRCTN68133435).

HIV-infected patients aged ≥18 years who were hospitalized with a first episode of CM diagnosed by CSF India ink and had received ≥3 doses of AmB were eligible for enrollment. CM was confirmed by CSF culture for C. neoformans. Patients were excluded for alanine aminotransferase levels >5 times upper limit of normal (>200 IU/L), absolute neutrophil count <500 × 10⁶ cells/L, platelet count <50,000 × 10⁶ platelets/L, pregnancy, lactation, previous serious reaction to study drugs, or prior or current use of antiretroviral therapy (ART).

Written informed consent was obtained from each patient or next of kin for patients with altered mental status (Glasgow coma scale <15).

**Interventions**

Patients were randomized individually using a computer-generated program to 1 of 4 treatment arms:

- **regimen 1**: AmB (0.7 or 1 mg/kg/day) plus flucytosine (25 mg/kg 4 times daily) for 2 weeks,
- **regimen 2**: AmB (0.7 or 1 mg/kg/day) plus fluconazole (800 mg daily) for 2 weeks,
- **regimen 3**: AmB (0.7 or 1 mg/kg/day) plus fluconazole (600 mg twice daily) for 2 weeks, and
- **regimen 4**: AmB (0.7 or 1 mg/kg/day) plus voriconazole (300 mg twice daily; 400 mg twice on day 1) for 2 weeks.

For patients unable to receive oral medication, the second-line agents were given by nasogastric tube. Randomization of patients receiving rifampicin was restricted to the first 3 arms of the study because of the significant interaction between rifampicin and voriconazole. Randomization was stratified by altered mental status at admission. After 2 weeks, patients in all treatment arms received fluconazole (400 mg daily for 8 weeks and 200 mg daily thereafter). These fluconazole consolidation and maintenance doses were increased by 50% in patients receiving concurrent rifampicin.

To reduce significant AmB-related anemia, patients were allocated to AmB (0.7 mg/kg/day or 1 mg/kg/day) according to their baseline hemoglobin level. Patients with a baseline hemoglobin level <8 g/dL received AmB (0.7 mg/kg), whereas patients with a hemoglobin level ≥8 g/dL received AmB (1 mg/kg). Unless contraindicated, patients received 1 L of 0.9% normal saline daily to minimize AmB nephrotoxicity. Potassium and magnesium were supplemented as required (20 mmol KCl was added to the 1 L normal saline, unless the serum potassium level was high). If the serum creatinine level increased to >2.5 mg/dL (220 µmol/L), despite adequate hydration and saline loading, AmB-based induction therapy was discontinued and the patient switched early to fluconazole consolidation therapy. 5-FC was adjusted for creatinine clearance according to standard protocols [17].

Follow-up lumbar punctures were performed on days 3, 7, and 14. Patients with CSF opening pressure >35 cm H₂O and/or headache or other symptoms attributable to increased pressure had additional lumbar punctures performed. After hospital discharge, participants were counseled, initiated on ART from 2 weeks after the start of antifungal therapy [18], and followed up for 6 months from study enrolment.

**Evaluation and Outcomes**

All participants had complete blood count, electrolyte level, urea and creatinine levels, liver enzyme levels, CD4 cell count, and
HIV load measured at baseline. Subsequently, renal function was evaluated on alternate days, and liver enzyme levels and full blood count were measured twice weekly.

CSF samples were analyzed for cell count and differential, protein, glucose, India ink, cryptococcal antigen titer, and quantitative fungal culture, as described elsewhere [16]. Cryptococcal clearance rates were calculated using a summary statistic for each patient, defined as the decrease in log CFU per mL CSF per day, with use of the slope of the linear regression of log CFU against time for each patient. Percentage change in laboratory values was calculated using the following formula: (final value-baseline value/baseline value) × 100.

The primary outcome measure was the mean rate of decrease in CSF cryptococcal CFU or EFA for each treatment arm. Secondary outcome measures were mortality at 2 and 10 weeks and drug-related clinical and laboratory adverse events.

Statistics

We compared baseline characteristics and outcomes in groups by the χ² or Fisher’s exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Linear regression was used to compare mean rates of decrease or EFA by treatment group, adjusting where indicated for other variables, giving summary differences with 95% confidence intervals (CIs) and significance levels. Laboratory adverse events and median percentage changes in laboratory values in treatment groups and among patients receiving the 2 doses of AmB were compared using the χ², Fisher’s exact, Kruskal-Wallis, or Mann-Whitney test, as appropriate. Analyses were performed using Stata, version 11 (Stata Corp).

RESULTS

Eighty patients with a first episode of culture-proven CM were enrolled (Figure 1). One patient in treatment group 3 was excluded from the study, because he was found to meet an exclusion criterion on study day 2 (previous episode of CM). One patient was lost to follow-up at 2–10 weeks in each of treatment arms 2, 3, and 4. One additional patient in study group 1 discontinued all medical intervention on study day 4 for personal reasons.

Baseline Characteristics

Baseline clinical and laboratory characteristics and clinical outcomes are shown in Table 1. 57 patients (72%) were known to be HIV seropositive before study enrolment. The median CD4 cell count was 24 × 10⁶ cells/L. Twelve patients (15%) had abnormal mental status (Glasgow coma scale <15) at baseline. Thirty-seven patients (47%) received 1–3 doses of AmB before study enrolment, and baseline fungal burden was significantly associated with exposure to AmB before study enrolment (P < .001). Of note, fewer patients in group 3 (30%) and more patients (62%) in treatment group 4 received AmB before enrolment, compared with the other treatment groups. Treatment group 3 had higher (median, 5.54 logCFU/mL CSF) and treatment group 4 lower (median, 4.49 logCFU/mL CSF) baseline fungal burdens (Table 1, P = .03). There were no other statistically significant differences among the 4 treatment arms with regard to established prognostic factors for CM (abnormal mental status, CSF white cell count, and CSF opening pressure) or HIV infection (CD4 cell count and HIV load).

EFA

There were no statistically significant differences in the rate of clearance of cryptococcal CFU from the CSF among the 4 treatment groups: the mean (± standard deviation) EFA for treatment groups 1, 2, 3, and 4 were −0.41 ± 0.22 log CFU/mL CSF/day, −0.38 ± 0.18 log CFU/mL CSF/day, −0.41 ± 0.35 log CFU/mL CSF/day, and −0.44 ± 0.20 log CFU/mL CSF/day, respectively, with no statistically significant difference among groups (P = .6, P = .9, and P = .7 for comparison of groups 2, 3, and 4 with group 1, respectively) (Figure 2).

In this dataset, rate of clearance was associated with weight (increase in rate of clearance, or slope, for each increase in weight quartile: 0.07 log CFU/day; 95% CI, 0.02–0.12; P = .006). After adjusting for weight and factors previously found to be associated with rate of clearance (baseline fungal burden, AmB dose, and CD4 cell count), there was still no statistically significant difference among treatment groups (adjusting for weight, comparing groups 2, 3, and 4 with group 1, differences in slope were: 0.03 log CFU/day [95% CI, −0.12 to 0.17; P = .7], −0.01 log CFU/day [95% CI −0.16 to 0.14; P = .9], and −0.01 log CFU/day [95% CI, −0.19 to 0.17; P = .9], respectively). For the 2 groups of patients receiving fluconazole (treatment groups 2 and 3), mean (± standard deviation) rate of clearance was −0.44 ± 0.32 log CFU/mL CSF/day for patients not receiving concurrent rifampicin treatment (n = 29) and −0.32 ± 0.17 log CFU/mL CSF/day for patients receiving concurrent rifampicin (n = 16; P = .2). Nine (43%) of 21, 7 (32%) of 22, 5 (22%) of 23, and 3 (23%) of 13 had negative culture results at day 14 in treatment groups 1–4, respectively.

Mortality

The overall mortality rate was 12% (9 of 78 died) at 2 weeks and 29% (22 of 75 patients died) at 10 weeks, with no statistically significant difference among treatment groups (Table 1). All surviving patients received ART at a median of 34 days after starting antifungal therapy.

Safety

There were no grade 3 or 4 adverse events thought to be related to the second drugs given with AmB (Table 2). In particular, there were no grade 3 or 4 decreases in neutrophil count that could have been related to 5-FC and no grade 3 or 4 increases
in alanine aminotransferase level that could have been related to fluconazole or voriconazole. The median (interquartile range) percentage change in neutrophil count did not differ comparing group 1 (21%; 23% to 25%) with the other groups (1%; 43% to 91%; P = .4). None of the 13 patients receiving voriconazole experienced adverse effects, such as visual disturbance or rash.

AmB-related anemia and renal impairment were common. There were no statistically significant differences among treatment arms in terms of percentage decrease in hemoglobin level or percentage increase in creatinine level during the first 2 weeks of study enrolment (data not shown). Eight (10%) of 79 patients discontinued use of study drugs before the end of week 2 because of AmB-related anemia or renal impairment.

Six patients (3 patients in group 2, 2 patients in group 4, and 1 patient in group 1) stopped study drugs early because of grade 4 anemia at study days 9, 10, 11 (2 patients), and 12 (2 patients). Two patients (1 patient each in group 1 and 4) experienced grade 3 and grade 2 renal impairment, respectively, and study drugs were stopped on study day 9 as a result.

On the basis of baseline hemoglobin level, 65 patients (82%) received AmB (1 mg/kg) and the remaining 14 patients with baseline hemoglobin level ≤8 g/dL (18%) received AmB (0.7 mg/kg). The median decrease in hemoglobin level over the first 2 weeks of therapy was 1.9 g/dL in the AmB 1 mg/kg group and 0.6 g/dL in the AmB 0.7 mg/kg group. The median percentage decrease in hemoglobin level in the amphotericin

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**Figure 1.** Patient flow chart. Abbreviations: 5-FC, flucytosine; AmB, amphotericin B; bd, twice daily; od, once daily; qds, four times daily.
DISCUSSION

More effective, easily administered, and readily available antifungal regimens for the treatment of CM are urgently needed. We found no statistically significant difference in EFA between the combination of AmB and high-dose fluconazole, a safe and readily available second-line agent, and the current standard of AmB and 5-FC therapy. The results support the use of AmB plus fluconazole at a dosage of at least 800 mg daily in Africa and elsewhere where 5-FC is not currently available, pending the results of a phase 3 clinical trial of combination therapy for CM conducted in Vietnam in which AmB alone is being compared with AmB plus 5-FC and AmB plus fluconazole 800 mg; (ISRCTN95123928).

Our findings are in keeping with animal model data that have demonstrated an additive effect of AmB and fluconazole [19, 20]. No prior studies have compared fluconazole at a dosage of $\geq 800$ mg/day with 5-FC as second-line agents with AmB. Brouwer et al showed a trend toward more rapid CSF sterilization with AmB plus fluconazole (400 mg daily; EFA, $-0.39 \log$ CFU/mL/day), compared with AmB alone (EFA, $-0.31 \log$ CFU/mL/day) [16]. Of note, in contrast to our findings using fluconazole at 800 mg daily or 600 mg twice daily, AmB plus fluconazole (400 mg daily) in that study was significantly less rapidly fungicidal than was AmB plus 5FC (EFA, $-0.54 \log$ CFU/mL/day). Pappas et al found that AmB (0.7 mg/kg) plus fluconazole (800 mg daily) had the highest response rates as assessed by a composite end point of survival, neurologic stability, and negative CSF culture results after 14 days, compared with AmB alone and AmB plus fluconazole (400 mg/day) [21]. AmB plus fluconazole (800 mg/day) was recently adopted as the standard induction antifungal regimen in a multicenter study being conducted at African sites on the timing of ART after therapy for CM (Cryptococcal Optimal Antiretroviral Therapy Timing [Coat Trial]; ISRCTN: NCT01075152).

Overall, the second-line drug was well tolerated in this clinical trial, with drug interruptions due to only AmB therapy. In particular, high-dose fluconazole was well tolerated with no adverse liver function abnormalities, in keeping with previous clinical trial data [22–26]. Of interest, there were no cases of grade 3 or 4 neutropenia in the 20 patients assigned to the AmB plus 5-FC arm. In prior studies by our group, 5-FC for 2 weeks at 100 mg/kg/day has been associated with grade 4 neutropenia in 6 (3.6%) of 163 patients (0 of 32 patients in Thailand [16], 3 of 41 of patients in Malawi [22], and 3 of 90 patients in Cape Town [27]). In our view, 5-FC can be used safely in centers in developing countries, with dose adjustment for any AmB-related renal impairment and complete blood count monitoring and no flucytosine level monitoring [28].

A role for voriconazole in the treatment of cryptococcosis has been supported by in vitro and animal model data [29–31]. Clinical data regarding the use of voriconazole for the

| Table 1. Baseline Clinical and Laboratory Characteristics and Clinical Outcomes for Treatment Groups 1–4 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristics | All patients | Group 1 AmB + 5-FC | Group 2 AmB + FLU 800 | Group 3 AmB + FLU 1200 | Group 4 AmB + VORI | $P$ values |
| No (%) of men | 39 (49) | 9 (43) | 11 (60) | 13 (57) | 6 (46) | .83 |
| Age (years) | 34 (29–39) | 34 (29–38) | 32 (29–38) | 33 (29–38) | 36 (33–40) | .59 |
| Weight (kg) | 56 (49–62) | 54 (46–63) | 56 (48–62) | 54 (49–61) | 60 (55–64) | .45 |
| No (%) of patients with known HIV | 57 (72) | 15 (71) | 17 (77) | 19 (83) | 6 (46) | .13 |
| No (%) of patients with abnormal mental status | 12 (15) | 3 (14) | 3 (13) | 4 (17) | 2 (15) | 1.0 |
| No (%) of patients with concurrent tuberculosis at enrollment | 24 (30.4) | 8 (38.1) | 5 (22.7) | 11 (47.8) | 0 (0) |
| CD4 cell count, X 10⁶ cells/L | 24 (9–43) | 13 (6.5–34) | 31 (17–70) | 24 (9–69) | 27 (9–36) | .26 |
| No (%) of patients dosed at AmB 0.7 | 14 (17.7%) | 4 (19) | 3 (13.6) | 5 (20.8) | 2 (15.3) | .93 |
| CSF data | | | | | | |
| Opening pressure, cmH20 | 18 (15–35) | 29 (15–39) | 17 (15–25) | 18 (15–35) | 25.5 (15.5–42) | .24 |
| WBC count, cells/mm³ | 19.5 (0–55.3) | 6 (0–50) | 10 (0–20) | 20 (0–68) | 30 (0–60) | .21 |
| Baseline fungal burden, logCFU/mL of CSF | 4.95 (3.79–5.64) | 4.83 (4.35–5.89) | 4.95 (3.75–5.46) | 5.54 (4.86–5.79) | 4.49 (3.48–4.82) | .03 |
| Death, no (%) of patients | | | | | | |
| By week 2 | 9/78 (11.5) | 1/20 (5) | 3/22 (13.6) | 4/23 (17.4) | 1/13 (7.7) | .60 |
| By week 10 | 22/75 (29) | 6/20 (30) | 7/21 (33.3) | 6/22 (27.3) | 3/12 (25) | .96 |

Abbreviations: 5-FC, flucytosine; AmB, amphotericin; CFU, colony-forming units; CSF, cerebrospinal fluid; FLU, fluconazole; HIV, human immunodeficiency virus; VORI, voriconazole; WBC, white blood cell.

* Values are median (IQR) unless otherwise stated.
treatment of cryptococcosis is otherwise limited to case reports and small series [14, 32–35]. To our knowledge, this study represents the first randomized, comparative clinical trial evaluating voriconazole for the treatment of HIV-associated CM. Thus, although the numbers of patients studied was small, it appears that the EFA of voriconazole in combination with AmB did not differ significantly from the EFA of high-dose fluconazole or 5-FC with AmB. The comparison of the voriconazole arm with the 3 other arms is potentially biased by the fact that only patients not receiving rifampicin could be randomized to receive voriconazole. However, the EFA for voriconazole (−0.44 log CFU/mL CSF/day) was the same as the mean EFA for the fluconazole arms in patients not receiving rifampicin (−0.44 log CFU/mL CSF/day). Voriconazole appeared to be well tolerated at 300 mg twice daily for 2 weeks. Voriconazole is useful and effective for rare patients whose isolates develop secondary fluconazole resistance [29, 31, 32, 35]. However, in addition to cost issues, where the

Figure 2. Decrease in number of cerebrospinal fluid Cryptococcus neoformans colony-forming units over time by treatment group. All patients received AmB-based therapy. Abbreviations: 5FC, flucytosine; CFU, colony-forming units; Flu, fluconazole; Vori, voriconazole.

Table 2. Serious Adverse Events Per Treatment Group

<table>
<thead>
<tr>
<th>Type/Grade of event</th>
<th>AmB + 5-FC</th>
<th>AmB + Fluc, 800 mg</th>
<th>AmB + Fluc, 1200 mg</th>
<th>AmB + Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade III</td>
<td>Grade IV</td>
<td>Grade III</td>
<td>Grade IV</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Transaminase elevation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FC, flucytosine; AmB, amphotericin B.
HIV and tuberculosis coinfection prevalence is high, use of voriconazole for the treatment of CM is limited by interactions with rifamycins [36] and is complicated by interactions with antiretroviral agents [37, 38].

As in a prior randomized study [39], the percentage decrease in hemoglobin level was greater in patients assigned to 1 mg/kg/day of AmB, compared with patients receiving 0.7 mg/kg/day. Although reversible, the clinical significance of AmB-associated anemia, especially in patients with low baseline hemoglobin level and in settings where transfusion is restricted, is unclear. Use of the 0.7 dose of AmB, with fluconazole, in patients with very low baseline hemoglobin level may prevent some grade 4 anemia, and it is possible this benefit may outweigh the reduction in rate of clearance of infection with the lower dose [39]. However, if AmB is given for <2 weeks, we would still favor the higher AmB dose, with complete blood count monitoring.

The overall mortality of 29% at 10 weeks supports the use of combination AmB-based therapy in Africa, as opposed to much less rapidly active fluconazole monotherapy (EFA, −0.02 to −0.18 log CFU/mL/day [22, 23, 40]), with an associated 10-week mortality of ≥50% ([22, 23, 41]) or AmB monotherapy (10-week mortality, 33%–43% [40, 42]), wherever feasible. In most centers in Africa and Asia, combination therapy will currently be with AmB and fluconazole. If a standard 2-week induction with AmB combination treatment is not possible, shorter durations of AmB-based induction therapy should be used in preference to fluconazole monotherapy. A trial in resource-limited settings that compares 1 week with 2 weeks induction with AmB plus fluconazole with optimized oral combination therapy with fluconazole plus 5-FC is planned.

Notes

Author contributions. A. L. conducted the trial, collected the data and wrote the manuscript. A. L., J. N. J. and T. S. H. analysed the data. T. B. and J. N. J. wrote the manuscript. A. L., J. N. J. and T. S. H. analysed the data. T. B. and J. N. J. and T. S. H. analysed the data. T. B. and J. N. J. and T. S. H. analysed the data. T. B. and J. N. J. and T. S. H. analysed the data.

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