Early Versus Delayed Antiretroviral Therapy and Cerebrospinal Fluid Fungal Clearance in Adults With HIV and Cryptococcal Meningitis

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Background. The burden of Cryptococcus neoformans in cerebrospinal fluid (CSF) predicts clinical outcomes in human immunodeficiency virus (HIV)-associated cryptococcal meningitis (CM) and is lower in patients on antiretroviral therapy (ART). This study tested the hypothesis that initiation of ART during initial treatment of HIV/CM would improve CSF clearance of C. neoformans.

Methods. A randomized treatment-strategy trial was conducted in Botswana. HIV-infected, ART-naive adults aged ≥21 years initiating amphotericin B treatment for CM were randomized to ART initiation within 7 (intervention) vs after 28 days (control) of randomization, and the primary outcome of the rate of CSF clearance of C. neoformans over the subsequent 4 weeks was compared. Adverse events, including CM immune reconstitution inflammatory syndrome (CM-IRIS), and immunologic and virologic responses were compared over 24 weeks.

Results. Among 27 subjects enrolled (14 control and 13 intervention), the median times to ART initiation were 7 (interquartile range [IQR], 5–10) and 32 days (IQR, 28–36), respectively. The estimated rate of CSF clearance did not differ significantly by treatment strategy (−0.32 log10 colony-forming units [CFU]/mL/day ± 0.20 intervention and −0.52 log10 CFUs/mL/day ± 0.48 control, P = .4). Two of 13 (15%) and 5 of 14 (36%) subjects died in the intervention and control arms, respectively (P = 0.39). Seven of 13 subjects (54%) in the intervention arm vs 0 of 14 in the control arm experienced CM-IRIS (P = .002).

Conclusions. Early ART was not associated with improved CSF fungal clearance, but resulted in a high risk of CM-IRIS. Further research on optimal incorporation of ART into CM care is needed.

Clinical Trials Registration. NCT00976040.

Keywords. HIV-1; cryptococcal meningitis; randomized controlled trial; Africa; highly active antiretroviral therapy (HAART).

Cryptococcal meningitis (CM), caused by the yeast Cryptococcus neoformans, is a devastating opportunistic infection that affects individuals with advanced human immunodeficiency virus (HIV) infection and results in approximately 600 000 deaths globally each year [1]. Nearly 10% of patients with CM in the developed world die despite optimal management [2], and in resource-limited settings mortality rates can exceed 50% [3–5].

Recent studies have demonstrated the benefits of early initiation of antiretroviral therapy (ART) in patients with tuberculosis [6–8]. The data informing ART timing are more limited for CM. Challenges to rapid ART initiation in CM include impaired cognition, overlapping toxicities of ART and antifungal therapy, and the immune reconstitution inflammatory syndrome (IRIS), which occurs in 10%–45% of
patients and may be fatal [9–14]. A recent trial from Zimbabwe was terminated early after demonstrating decreased survival in individuals with HIV/CM who were initiated on ART within 72 hours vs after 10 weeks from initial CM treatment [14]. In contrast, the AIDS Clinical Trials Group Study 5164, which included 35 subjects with CM, found fewer deaths and AIDS progression events in those treated with early vs deferred ART [15]. Thus, further studies are needed.

The rate of clearance of C. neoformans from cerebrospinal fluid (CSF) has been associated with mortality, and clearance is facilitated by use of combination antifungal therapy [16, 17]. Thus, current guidelines recommend amphotericin B and fluconazole as first-line therapy based, in part, on improved CSF clearance using both agents vs amphotericin B alone [2, 18, 19]. However, fluconazole is unavailable in many resource-limited settings where CM is common. Adjunctive interferon gamma (IFN-γ) administration improves CSF clearance in HIV-infected patients with CM [20], patients with CM on ART have lower CSF fungal burden compared to those not on ART [21, 22], and greater C. neoformans–specific immune responses have been associated with improved CM survival [23]. We therefore hypothesized that ART, considered as adjuvant therapy during the acute phase of CM, would mediate more rapid CSF clearance of C. neoformans.

METHODS

Ethical Approvals
The institutional review boards of the Botswana Ministry of Health, the Princess Marina Hospital, and the University of Pennsylvania School of Medicine approved this study.

Trial Design
This study was an open-label treatment strategy trial randomizing subjects with HIV/CM 1:1 to immediate (“intervention”) vs standard (“control”) timing of ART initiation. The intervention group had ART initiated within 7 days of randomization, whereas the control group started ART after 28 days postrandomization. Randomization occurred within 72 hours after the initiation of antifungal therapy.

The primary study outcome was the rate of clearance of C. neoformans from CSF over the first 28 days after randomization. Subjects were followed for up to 24 weeks after the planned date of ART initiation in order to compare the incidence of grade 3 and 4 adverse events (AEs) and serious AEs, and the changes in CD4 cell counts and HIV RNA levels (viral load), during follow-up.

Study Setting
This study was set in the sub-Saharan African country of Botswana. The first study site was the Princess Marina Hospital, the main public hospital in the capital city, Gaborone. Two other hospitals were added later: Scottish Livingstone and Bamalete Lutheran Hospital, both located in the greater Gaborone area. These 3 hospitals are public referral hospitals serving a population where the HIV prevalence is 17% and the short-term mortality rate of patients with HIV and CM is nearly 20% [21, 24].

Study Subjects
Adults ≥21 years of age were eligible if they (1) were HIV-infected, as documented by a positive enzyme-linked immunosorbent assay and/or a detectable (ie, >400 copies/mL) plasma viral load; (2) were admitted with India ink–positive CM; (3) were ART-naive, defined as no past use of ART for prevention of mother-to-child transmission ≥6 months previously; (4) could provide written informed consent; (5) were to initiate or had initiated amphotericin B ≤72 hours prior to enrollment; (6) reported no antifungal use within the prior 14 days; (7) were not pregnant, as determined by a negative urine β-human chorionic gonadotropin test, or were breastfeeding; (8) had not initiated antitubercular therapy ≤2 weeks prior to assessment; (9) did not have bacterial meningitis; (10) were deemed unlikely to initiate immunomodulatory therapy (eg, cancer chemotherapy) prior to the week 4 study visit; (11) were not prisoners; (12) had available CSF for determination of baseline colony-forming units (CFUs); and (13) would obtain outpatient care within the logistical reach of the study team.

Study Treatments
Care in the study was given by the local providers. According to Botswana National Guidelines, subjects of nonreproductive potential initiate combination tenofovir (TDF)/emtricitabine (FTC) and efavirenz (EFV), whereas women of reproductive potential receive TDF/FTC and nevirapine (NVP). Guidelines also recommend cotrimoxazole for patients with CM. Standard CM treatment is amphotericin B 0.7 mg/kg × 14 days, followed by oral fluconazole 400 mg daily × 8 weeks, followed by oral fluconazole 200 mg daily until the CD4 count is >200 cells/μL for 6 months.

Data Collection
All study-specific visits, performed at entry and then at days 7 and 14, week 4, and monthly thereafter, included medical history and physical examination. Incident AEs were graded using the Division of AIDS Table for Grading Adult Adverse and Pediatric Adverse Events [25]. HIV load, CD4 count, and complete blood count were performed at randomization, at week 4, and then at weeks 12 and 24 after the planned date of ART initiation. Serum chemistries were performed as above and at days 7 and 14. A South African National Accreditation...
System-accredited clinical lab performed all clinical lab assays. Fungal CFUs were performed using a standard protocol [17] on the initial CSF sample submitted for diagnosis, on CSF obtained at a study-specific lumbar puncture performed 4 weeks after randomization, and on available CSF obtained from other lumbar punctures. Cases of CM-IRIS were defined by 2 research team physicians (M.M. and S.G.) in an unblinded manner using the definition proposed by Haddow et al [26] and were categorized as definite (meeting all criteria) or possible.

**Statistical Analyses**

Characteristics were compared using the Student t test or Wilcoxon rank-sum test or the χ² or Fisher exact test. Time to event outcomes were examined using Kaplan-Meier analyses and log-rank tests. The rate of fungal clearance was determined using the slope of the estimated linear regression model coefficient relating average change in CSF CFUs over time, where CSF CFUs were log₁₀ transformed and negative CSF cultures were given a value of 1, as described [17]. We used a generalized estimating equation model, which accounts for within-subject correlation from repeated measures on subjects over time [27], to compare the rate of CSF clearance between arms. In addition, we determined the proportion of all subjects who achieved a negative CSF culture at week 4 or an undetectable viral load at week 24, classifying missing values as failure to achieve these surrogate outcomes at these timepoints. The cumulative incidence and 95% confidence interval (CI) of clinical events were reported for the period of follow-up occurring within 24 weeks from randomization (ie, not including the additional follow-up accumulated by controls). Analyses were performed using Stata version 11.0 (StataCorp, College Station, Texas).

**Sample Size Calculation**

We powered the study a priori to detect an effect of ART on clearance that is equal to or greater than the effect of flu cytosine when added to amphotericin B (ie, −0.23 log₁₀ CFU/mL/day) [17]. To have 80% power, we needed to enroll 14 subjects per group, and targeted 25 per group to provide balance in clinical characteristics across arms. The study was stopped prior to achieving this number because of difficulties enrolling and funding limitations.

**RESULTS**

**Baseline Characteristics**

The study enrolled 28 subjects between 22 September 2009 and 26 April 2011. The last subject completed the study in November 2011. Twenty-two, 2, and 4 subjects were enrolled at Princess Marina Hospital, Scottish Livingstone Hospital, and Bamalete Lutheran Hospital, respectively. One subject randomized to the intervention withdrew consent immediately after randomization and is not included in analyses (Figure 1). No subjects were lost to follow-up.

Baseline demographic and clinical characteristics are shown in Table 1. The median baseline CD4 count was 29 cells/µL (interquartile range [IQR], 11–50), and the median baseline CD4 counts and hemoglobin values were slightly lower among the control subjects (Table 1, rank-sum P values for both >.20). The median initial Glasgow Coma Scale for all subjects was 15. The median log₁₀ C. neoformans CFU/mL at baseline was 5.7 (IQR, 5.2–6.5), and was not significantly different by arm (Table 1; P > .5, rank-sum test).

**ART Initiation**

Twelve of 13 (92%) subjects in the intervention arm and 10 of 14 (71%) subjects in the control arm initiated ART during the study. Eighteen (82%) subjects initiated combination TDF/FTC/EFV, whereas the remaining 4 subjects initiated combination zidovudine/lamivudine plus NVP or EFV (2 subjects) or TDF/FTC and NVP (2 subjects). The median times to ART initiation were 7 days (IQR, 5–10) and 32 days (IQR, 28–36) after randomization in the intervention and control arms, respectively. All control subjects not initiating ART died before their scheduled date of ART initiation.

**Mycologic Outcomes**

**CSF Clearance**

Eleven of 14 (79%) and 12 of 13 (92%) subjects in the control and intervention arms, respectively, had 1 or more CSF CFU values obtained after amphotericin B initiation to week 4. Baseline and changes in CSF CFUs are shown in Figure 2. The median numbers of CSF CFU measurements obtained during this interval for the control and intervention arms, respectively, were 3 (IQR, 2–4 [range, 1–9]) and 4 (IQR, 2–5 [range, 1–7]) (P = .2, rank-sum test). Using linear regression, the median estimated rate of CSF clearance was −0.42 log₁₀ CFU/mL/day (±0.37) for the cohort overall (intervention arm: −0.32 log₁₀ CFU/mL/day ±0.20, and control arm: −0.52 log₁₀ CFU/mL/day±0.48; P = .4). The generalized estimating equation regression coefficient for the intervention was 0.20 (95% CI, −.85 to 1.25), indicating that intervention subjects had a rate of CSF clearance that tended to be 0.20 log₁₀ CFU/mL/day slower than controls, although this difference was not significant.

**CSF Cultures at Week 4**

One subject in each arm surviving to week 4 refused the week 4 lumbar puncture. Among those with week 4 cultures, 3 of 12 (25%) vs 0 of 9 in the intervention and control arms, respectively, had positive CSF cultures at week 4 (P = .2, Fisher
exact test). Thus, 4 of 13 subjects (31%) in the intervention arm and 5 of 14 (36%) subjects in the control arm did not achieve a documented negative week 4 CSF culture ($P > .5$, Fisher exact test). The 3 subjects with nonsterile fungal cultures at week 4 had 3.7, 4.3, and 5.3 log_{10} decreases in CFUs from baseline, respectively, at week 4.

Table 1. Baseline Characteristics of Study Subjects Overall and by Treatment Arm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 27)</th>
<th>Intervention (n = 13)</th>
<th>Control (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, No. (%)</td>
<td>14 (52)</td>
<td>7 (54)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Age, y (IQR)</td>
<td>35 (32–41)</td>
<td>34 (29–37)</td>
<td>38 (32–44)</td>
</tr>
<tr>
<td>CD4, cells/mm$^3$ (IQR)</td>
<td>29 (11–50)</td>
<td>36 (25–44)</td>
<td>14 (4–50)</td>
</tr>
<tr>
<td>HIV RNA, log$_{10}$ (IQR)</td>
<td>5.6 (5.0–6.0)</td>
<td>5.6 (5.1–5.8)</td>
<td>5.5 (4.9–6.2)</td>
</tr>
<tr>
<td>Hemoglobin*, g/dL (n = 24) (IQR)</td>
<td>10.7 (9.5–11.6)</td>
<td>11.2 (9.8–11.6)</td>
<td>9.9 (9.3–11.2)</td>
</tr>
<tr>
<td>Creatinine level, umol/L (IQR)</td>
<td>68.5 (62.2–89.4)</td>
<td>67.4 (64.9–85.0)</td>
<td>70.1 (61.5–89.4)</td>
</tr>
<tr>
<td>Potassium level, mmol/L</td>
<td>3.2 (2.8–3.8)</td>
<td>3.4 (3.0–3.8)</td>
<td>3.1 (2.6–3.3)</td>
</tr>
<tr>
<td>C. neoformans CFU (IQR)</td>
<td>480 000 (171 000–3 400 000)</td>
<td>1 370 000 (92 500–3 400 000)</td>
<td>437 500 (210 000–2 200 000)</td>
</tr>
<tr>
<td>C. neoformans CFU, log$_{10}$ (IQR)</td>
<td>5.7 (5.2–6.5)</td>
<td>6.1 (5.0–6.5)</td>
<td>5.6 (5.6–6.3)</td>
</tr>
<tr>
<td>Baseline OIs</td>
<td>22 (81)</td>
<td>10 (77)</td>
<td>12 (86)</td>
</tr>
</tbody>
</table>

Data are median interquartile range unless otherwise specified.

Abbreviations: CFU, colony-forming unit; IQR, interquartile range; OIs, other noncryptococcal opportunistic infections.

* Hemoglobin values available for 12 subjects in each arm.
Death and AIDS Progression Events by Arm

The 2- and 10-week cumulative mortality estimates for the cohort overall were 15% (14%–34%) and 22% (9%–42%), respectively. Two of 13 (15%) and 5 of 14 (36%) subjects died in the intervention and control arms, respectively, within 24 weeks of randomization (P = .39, Fisher exact test). Four of 5 deaths in the control arm occurred within 11 days, whereas the 2 deaths in the intervention arm occurred at 33 and 142 days after randomization (Supplementary Figure 1). One subject (4% of 27) in the control arm discontinued fluconazole and had a CM relapse. The incidence of AIDS progression events did not differ by arm (Table 2).

Virologic and Immunologic Responses

Subjects in the intervention arm experienced significantly greater reductions in viral load and increases in CD4 counts by week 4 (Table 2). Virologic and immunologic responses thereafter did not differ across arms (Table 2).

Adverse Events

All subjects (100%) in the intervention arm and 13 of 14 subjects (93%) in the control arm experienced 1 or more incident grade 3 or 4 AEs or serious AEs over 24 weeks of follow-up (Table 3). The median number of lumbar punctures attempted during the 24-week follow-up period was similar across the 2 arms (8 [IQR, 6–8] in immediate vs 9 [IQR 5–14] in control arms, P > .5, rank-sum test). Supplementary Table 1 provides clinical details of deaths and hospital readmissions during the study period. None of the patients who initiated NVP-containing ART experienced grade 3 or 4 hepatic AEs.

CM-IRIS

Seven of 22 subjects (33%) who initiated ART experienced CM-IRIS during follow-up (4 definite, 3 possible), with a median estimated onset from ART initiation of 9 days (range, 5–87 days). All cases occurred in the intervention arm (7 of 13 [54%] vs 0 of 14; P = .002, Fisher exact test). Three patients had negative CSF cultures, 1 had a CSF CFU count of 10/mL, 1 refused a lumbar puncture, and the other 2 had >2.0 log_{10} decreases in CSF CFU/mL at the time of IRIS. No subjects received corticosteroids. Four subjects’ CM-IRIS events were associated with hospital readmission, and both deaths in the intervention arm were associated with CM-IRIS (Supplementary Table 1).

DISCUSSION

Main Findings

In this randomized treatment strategy trial, we hypothesized that initiation of ART very early during acute CM disease would mediate more rapid clearance of *C. neoformans* from the CSF in subjects initiating amphotericin B for HIV-associated CM. Although this strategy did result in marked early virologic suppression and CD4 count increase by week 4, we found a trend without statistical significance toward delayed fungal clearance with early ART.

Immune restoration improves rapidly during ART [28–30], leading to greater polyfunctional *C. neoformans*–specific immune responses, which are associated with improved survival in HIV/CM [23]. Additionally, IFN-γ administration has been shown to improve fungal CSF clearance in patients with HIV/CM [20]. However, factors that improve pathogen control in CM likely are most effective when administered when pathogen levels are still high. The intervention was therefore purposefully aggressive in terms of ART timing; however, time to ART initiation in the intervention arm was still at the late end of our design. Logarithmic declines in

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**Figure 2.** Decline in cerebrospinal fluid colony-forming units over time for intervention and control arms in human immunodeficiency virus–infected patients treated for cryptococcal meningitis. Abbreviations: CFU, colony-forming unit; CSF, cerebrospinal fluid; QCC, quantitative cryptococcal culture.
C. neoformans CFUs occur quickly (Figure 2 and references [16, 31]), leaving little room for additional improvements in pathogen clearance potentially mediated by ART. Thus, although our data do not support the strategy, we cannot exclude the possibility that even earlier ART might be more effective in this regard. Earlier ART would, however, need to overcome considerable barriers including, for example, nausea and vomiting.

Although the study was not powered to compare clinical events, deaths were less common in those assigned to the intervention. While not statistically significant, this is notable given data showing the opposite effect in a Zimbabwean study [32] and in another large trial that was recently stopped because of increased mortality in the early ART arm [33]. Use of amphotericin B and not the less effective drug fluconazole [34], exclusion of patients unable to consent (who likely are at highest risk of death), and use of repeated lumbar punctures may explain these differences. The data also suggest that further research on timing of ART in CM is needed, as early ART initiation with close follow-up and aggressive disease management in patients with normal Glasgow coma scores on amphotericin B may be a viable strategy in selected individuals.

Importantly, however, several of the patients in the intervention arm experienced CM-IRIS, which may be severe [11, 12, 14, 26]. The finding that earlier ART was associated with CM-IRIS is consistent with some [12, 35] but not other studies [9, 11]. Timing of ART plausibly relates to the antigen burden at the time of ART initiation, and antigen levels have been associated with CM-IRIS in a large prospective study [9]. Thus, careful follow-up for CM-IRIS should be pursued in all patients with CM starting ART and particularly in those who initiate when antigen levels are high. Until further data emerge, we, like others [11], suggest that providers focus on

| Table 2. Outcomes in the Trial Overall and by Treatment Arm |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Outcome**                      | **Total (%) (N = 27)** | **Intervention (n = 13)** | **Control (n = 14)** | **P Value***   |
| Mycologic endpoints              |                  |                  |                  |                |
| Change in CSF CFU, baseline to week 4, CFU/mL (IQR) | 455 000 (171 000–3 100 000) | 2 010 000 (49 750–3 574 905) | 420 000 (355 000–1 950 000) | .11 |
| Sterile CSF culture at 4 wk, No. (%) | 18/21 (85%) | 9/12 (75%) | 9/9 (100%) | >.5 |
| Clinical endpoints               |                  |                  |                  |                |
| Death within 24 wk of randomization, No. (%) | 7 (26%) | 2 (15%) | 5 (36%) | .39 |
| Death or AIDS progression, No. (%) | 15 (56%) | 6 (46%) | 9 (64%) | .45 |
| HIV VL decrease at 4 wk after enrollment, log₁₀ copies/mL (IQR) | 2.0 (0.5–2.7) | 2.6 (2.2–3.0) | 0.3 (0.09–0.7) | <.001 |
| HIV VL <400 copies/mL at 24 wk | 14 (52%) | 8 (62%) | 6 (43%) | .32 |
| CD4 count 12 wk after planned date of ART, cells/µL (IQR) | 138 (89–177) | 124 (85–165) | 153 (121–196) | .48 |
| CD4 count 24 wk after planned date of ART, cells/µL (IQR) | 141 (98–163) | 133 (93–169) | 141 (102–156) | >.5 |
| Safety outcomes                 |                  |                  |                  |                |
| Readmissions, No. (%) | 6 (22%) | 4 (31%) | 3 (21%) | >.5 |
| Prolonged hospitalizations, No. (%) | 6 (22%) | 2 (15%) | 4 (29%) | .38 |

Abbreviations: ART, antiretroviral therapy; CFU, colony-forming units; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IQR, interquartile range; VL, viral load.

* All P values comparing continuous variables are for rank-sum tests.
acute CM disease management and initiate ART after the acute phase has passed.

**Strengths of the Study**

This study adds to a sparse literature on timing of ART in HIV/CM. The patient characteristics and mortality rates we identified are similar to those reported elsewhere in Africa and indicate the study’s generalizability [16, 17, 20, 31, 36]. Another strength relates to the assessments of fungal CFUs at time of recurrence of symptoms after ART initiation, which facilitates the diagnosis of CM-IRIS [26].

**Limitations**

The small sample size hindered comparisons of clinical events across arms and reduces our ability to control for confounding. This deficiency may be due in part to the high rate of ART coverage that Botswana has recently achieved [37], which reduces late-stage complications of AIDS [38, 39]. Although epidemiologic data are needed to confirm this, we suspect that CM incidence in Botswana has declined. Similarly, our study required patients to be ART-naive, and a large number of CM cases we assessed were occurring in patients who had recently initiated or defaulted ART. As ART coverage in sub-Saharan Africa expands, the number of patients with AIDS-related opportunistic infections who are ART experienced should increase, making management of these complex patients increasingly important. Another limitation is the use of therapeutic as opposed to protocol-driven lumbar punctures to estimate fungal clearance; however, because the number of therapeutic lumbar punctures was similar across arms, we believe this bias is unlikely to have substantially affected the results.

In conclusion, earlier ART initiation in HIV/CM did not improve mycologic outcomes in this trial. Further research on the optimal timing of ART in HIV/CM is urgently needed.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.
Notes

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Author contributions. G. P. B., P. T., and D. W. designed the study. All authors contributed to data collection or its supervision. G. P. B. and S. B. conducted the data analysis. G. P. B. drafted the first version of the paper, and all authors contributed to finalizing the report prior to publication.

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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