Published in final edited form as:

J Acquir Immune Defic Syndr. 2008 October 1; 49(2): 227–229. doi:10.1097/QAI.0b013e318183181e.

The Use of HAART Is Associated With Decreased Risk of Death During Initial Treatment of Cryptococcal Meningitis in Adults in Botswana

Gregory P. Bisson, MD, MSCE*, Rudo Nthobatsong, RN*, Rameshwari Thakur, MD*, Gloria Lesetedi, RN*, Kavita Vinekar†, Pablo Tebas, MD*, John E. Bennett, MD‡, Stephen Gluckman, MD*, Tendani Gaolathe, MD§, and Rob R. MacGregor, MD*

*Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

†University of Pennsylvania, Philadelphia, PA

‡Clinical Mycology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD

§Infectious Disease Care Clinic, Botswana

Abstract

Objective—The objective of this study was to evaluate outcomes among adults with a first episode of cryptococcal meningitis (CM), comparing those on highly active antiretroviral therapy (HAART) with those not on HAART.

Methods—We conducted a prospective cohort study among HIV-infected adults (aged 18 years and older) with a first episode of CM at the Princess Marina Hospital, in Gaborone, Botswana. The proportions surviving to discharge were compared. Logistic regression was used to evaluate the relationship between HAART use and risk of death in the hospital, adjusting for potential confounders.

Results—Ninety-two patients [median CD4 41 cells/mm³ (inter-quartile range 22–85)] were included, 26 of whom were on HAART at the time that they developed CM. The in-hospital mortality was lower among those on HAART {2 of 26 (8%) vs 14 of 66 (21%); odds ratio = 0.36 [95% confidence interval (CI) 0.09 to 1.49]}, and this result was statistically significant after adjustment for male sex and tuberculosis [adjusted odds ratio = 0.19 (95% CI 0.04 to 1.00)].

Conclusions—HAART use at the time of a first admission with CM is associated with decreased risk of death during the acute phase of disease. Reasons for this association should be explored.

Keywords

cryptococcal meningitis; HAART; Africa; cohort study

INTRODUCTION

The use of highly active antiretroviral therapy (HAART) in patients with active cryptococcal meningitis (CM) may be associated with severe pathologic inflammatory events characterized as the immune reconstitution inflammatory syndrome.¹⁻⁴ HAART-induced immune restoration in the presence of active CM could however improve patient survival, even if symptomatic worsening occurs, perhaps via HAART-mediated restoration of effective cell-mediated immunity and more rapid clearance of the pathogen. To begin examining these issues, we compared patient survival according to whether or not individuals were on HAART at the time of initial diagnosis of CM among HIV-infected patients with CM in Botswana.

METHODS

This study was set at the Princess Marina Hospital, which is the main tertiary care hospital serving Gaborone, the capital of Botswana. During the study period, we prospectively tested all cerebrospinal fluid (CSF) submitted to the National Health Laboratory for evaluation of suspected meningitis (as determined by the admitting physician) for presence of *Cryptococcus neoformans* using a qualitative cryptococcal antigen assay (CALAS; Meridian Diagnostics, Cincinnati, OH) and fungal culture. Cultures were performed using Sabouraud agar and incubated in a cooled incubator at 32°C for not less than 7 days. A positive result on either test (defined as >1:8 for the antigen assay) was used to diagnose CM. Before the study, 100 blind CSF specimens from patients who had had lumbar punctures were cultured in parallel for presence of *C. neoformans* at the National Health Laboratory and at the Clinical Mycology Laboratory of the National Institutes of Health, showing >95% concurrence in culture results.

Protocol for care of patients with CM at Princess Marina Hospital is as follows: amphotericin B deoxycholate (Fungi-zone; Bristol-Myers Squibb Co., Tokyo, Japan) is given at a dosage of 1 mg/kg/d for 14 days (which can be extended if clinicians feel further therapy is needed) preceded by 1 L of normal saline solution. At the end of amphotericin B therapy, patients were given oral fluconazole (Diflucan; Pfizer, New York, NY) of 400 mg/d for 8 weeks, followed by secondary prophylaxis with fluconazole 200 mg/d. Patients have an initial lumbar puncture for diagnosis with measurement of opening pressure and receive subsequent lumbar punctures as needed for increased pressure, as guided by Infectious Disease Society of America guidelines.⁵

We approached all HIV-infected adults aged older than 18 years with CM for informed consent, which was discussed in Setswana by a study nurse. Data were collected from patients and by reviewing outpatient medical records prospectively using a standardized data collection form designed for the study. Use of HAART and a history of CM or pulmonary tuberculosis were determined by asking the patient and/or the patient's family and by searching the paper and electronic medical records, both of which note patient medication (including HAART and fluconazole) drug names and dispensation dates. Patients were then followed during their inpatient stay until discharge to collect treatment information and outcomes. We limited analyses to patients with a first admission for CM. The primary outcome of interest was death in the hospital.

Statistical analyses were performed using STATA, version 9.1 (College Station, TX). Categorical variables were compared using Fisher exact test, and continuous variables were compared using *t* tests (if normally distributed) or rank sum tests. Given the cohort study design, a point estimate and 95% confidence interval (CI) for the relative risk (RR) of death among those on HAART were determined in an unadjusted analysis. However, to examine

the effects of confounding, we also used logistic regression analysis [which produces odds ratios (ORs)] to present the results. Factors significantly associated with death at a level of 0.20 or less (using Fisher exact *P* value) in an unadjusted analysis were included in the multi-variable model.⁶ Factors that changed the unadjusted OR by 15% or more were retained in the final adjusted model. The study was approved by the Institutional Review Boards at the Princess Marina Hospital and at the University of Pennsylvania.

RESULTS

In total, there were 127 admissions of CM that occurred among 106 patients who consented for the study during the period from May 31, 2005, to August 6, 2006. Twenty-one (18%) of these were repeat admissions, and 3 patients were admitted 3 times during the study period and are not included in the analyses. The remaining 92 (87% of the total) were admitted with their first episode of CM. Of these, disease was confirmed by CSF culture in all cases; 84 (91%) were India ink positive, and 87 (95%) were positive for CSF cryptococcal antigen. None had record of fluconazole use in the past.

Twenty-six patients (28%) were on HAART at the time that they developed CM. In all cases, HAART consisted of 2 nucleoside reverse transcriptase inhibitors plus a nonnucleoside reverse transcriptase inhibitor. The median time between HAART initiation and presentation with CM was approximately 3 months [93 days, interquartile range (IQR) 47–310].

Patients on HAART at the time of diagnosis of CM were more likely to be men and were slightly younger than those not on HAART, but the 2 groups were otherwise similar (Table 1). The number of days of amphotericin B therapy did not differ according to HAART status [14 days (IQR 9–14) vs 14 days (IQR 12–14); *P* > 0.50]. Seventy-three of the 92 patients (79%) had a CD4 count available from within 2 months of the admission date (median interval between admission date and date of the CD4 count = 0 day). The median CD4 count for the group overall was 41 cells/mm³ (IQR 22–85). Although the median CD4 count for those on HAART was slightly higher than those not on HAART at the time of admission, this difference was not statistically significant (Table 1).

Of the 92 patients, 16 (17%) died during their inpatient stay. The proportion of patients dying in the hospital was lower among those on HAART [2 of 26 (8%) vs 14 of 66 (21%); RR = 0.36 (95% CI 0.09 to 1.49)], but this difference was not statistically significant in the unadjusted analysis [OR = 0.31 (95% CI 0.07 to 1.47)]. Male sex [RR = 1.91 (95% CI 0.78 to 4.68), Fisher exact *P* = 0.17] and concomitant tuberculosis [RR = 2.42 (95% CI 0.87 to 6.75), Fisher exact *P* = 0.14] were the only factors found to be actual confounders. The CD4 count at the time of admission (dichotomized as above or below 50 cells/mm³ or analyzed as a continuous measure) was not a confounder (results not shown). The association between in-hospital mortality and use of HAART became statistically significant after adjusting for male sex and tuberculosis [adjusted OR = 0.19 (95% CI 0.04 to 1.00)].

DISCUSSION

This study suggests that patients on HAART at the time of a first diagnosis of CM have lower in-hospital mortality during initial therapy when compared with patients who are not on HAART at this time.

The study is strengthened by prospective data collection, which allowed us to obtain valid data on current HAART use and to assess potential confounders (eg, differences in administration of treatments for CM) that could have affected patient outcomes and biased the results. The study is also strengthened by use of a validated laboratory to perform

cryptococcal diagnostics. In addition, although several past studies have examined treatment outcomes primarily among patients initiating HAART in the setting of known CM,^{2,3} this study represents to our knowledge the largest examination to date of treatment outcomes of patients who develop a first episode of culture-positive CM while on HAART, which is consistent with previously used definitions of unmasking immune reconstitution inflammatory syndrome.¹

Bicanic et al,⁷ in South Africa, recently documented improved survival among HIV-infected adults with CM diagnosed while on HAART, although this difference was not manifested until 10 weeks after diagnosis. This study differs, in that we document a decreased risk of death in the HAART group during the initial therapy of disease. In both studies, it is possible that improved survival in patients on HAART was due to earlier detection of meningitis, which may relate to patients on HAART being in medical care. Although neither study found less advanced CM at the time of admission in patients on antiretrovirals, the fact that baseline CSF cryptococcal loads were significantly lower in the HAART-experienced group in South Africa (34,000 vs 235,000 colony forming units/mL CSF, $P = 0.03$) suggests that this may have been the case.⁷ An alternative explanation is that HAART-induced improvements in cell-mediated immunity lead to more effective control of yeast growth in CSF and more rapid clinical improvement after initiation of antifungal therapy.⁸ Although it would have been interesting to investigate this hypothesis further by obtaining data on the rapidity of CSF culture conversion, lumbar punctures were not performed specifically as part of the study protocol.

This study has several important limitations. Although prospective, the study was small and observational, and thus residual confounding in the results cannot be ruled out. Furthermore, although the point estimates of inpatient mortality seemed substantially different for those on and off HAART, actual statistical significance was only obtained after adjustment for the 2 confounders in the study—male sex and tuberculosis. As such, the results should be confirmed in larger samples and other settings. We also cannot be certain that some patients with severe CM on HAART died before hospital admission. However, it would seem that patients on HAART are likely to have disease detected at least as often as patients not on HAART because the former group are by definition receiving medical care.

Most importantly, this study cannot answer the question of when to start HAART in patients with CM. HAART initiation during initial treatment of CM could be associated with both beneficial and adverse effects. Very early HAART initiation may improve organism control via early immune recovery, which may in turn decrease recurrence and improve survival. If true, then HAART could be considered as an adjuvant therapy for CM, acting in addition to initial conventional antifungal therapy to improve clearance of yeast from CSF. This could be particularly important in resource-limited settings where HAART but not amphotericin B is available and initial therapy is the less fungicidal drug fluconazole. Alternatively, very early HAART initiation could increase risk of pathologic inflammation and cerebral edema, leading to worse outcomes compared with delaying HAART. Although limited, these data suggest that there is a protective effect of HAART that is manifested very early in the course of CM. As such, clinical trials evaluating the role of very early HAART initiation on outcomes should be pursued.

Acknowledgments

G.P.B., T.G., and R.M. designed the study. R.N., R.T., and G.L. collected the data. J.E.B. performed evaluation of diagnostics at the National Health Laboratory by testing samples sent to the National Institutes of Health from Botswana. His contribution was supported by the intramural program of the National Institute of Allergy and Infectious Diseases. G.P.B. was responsible for data analysis and writing the first draft of the manuscript. All authors contributed comments to the work and assisted in writing the final version.

REFERENCES

1. Jenny-Avital ER, Abadi M. Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. *Clin Infect Dis*. 2002; 35:e128–e133. [PubMed: 12471589]
2. Shelburne SA III, Darcourt J, White AC Jr, et al. The role of immune reconstitution inflammatory syndrome in AIDS-related *Cryptococcus neoformans* disease in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2005; 40:1049–1052. [PubMed: 15825000]
3. Lortholary O, Fontanet A, Memain N, et al. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. *AIDS*. 2005; 19:1043–1049. [PubMed: 15958835]
4. Lawn SD, Bekker LG, Myer L, et al. Cryptococcal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. *AIDS*. 2005; 19:2050–2052. [PubMed: 16260920]
5. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis*. 2000; 30:710–718. [PubMed: 10770733]
6. Cepeda MS, Boston R, Farrar JT, et al. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol*. 2003; 158:280–287. [PubMed: 12882951]
7. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naïve or antiretroviral-experienced patients treated with amphotericin B or fluconazole. *Clin Infect Dis*. 2007; 45:76–80. [PubMed: 17554704]
8. Siddiqui AA, Brouwer AE, Wuthiekanun V, et al. IFN-gamma at the site of infection determines rate of clearance of infection in cryptococcal meningitis. *J Immunol*. 2005; 174:1746–1750. [PubMed: 15661940]

TABLE 1

Characteristics of Patients Admitted to Princess Marina Hospital With CM, Gaborone, Botswana

Characteristic (n = 92)	On HAART (n = 26)	Not on HAART (n = 66)	Association*
Age, mean yrs (range)	33 (20–45)	37 (20–65)	<i>P</i> = 0.06
Male sex, n (%)	17 (65)	20 (30)	<i>P</i> = 0.002
Tuberculosis, n (%)	2 (8)	6 (9)	<i>P</i> > 0.50
Symptoms			
Headache, n (%)	25 (96)	63 (95)	<i>P</i> > 0.50
Duration of headache, median d (IQR)	6 (3–7)	6 (3–7)	<i>P</i> > 0.50
Meningismus, n (%)	24 (92)	61 (92)	<i>P</i> > 0.50
Fever, n (%)	23 (68)	57 (79)	<i>P</i> = 0.20
Cough, n (%)	11 (42)	24 (36)	<i>P</i> > 0.50
Abnormal GCS, n (%)	2 (8)	9 (14)	<i>P</i> > 0.50
CD4 counts, cells/mm ³ , median (IQR)	52 (24–114)	41 (21–85)	<i>P</i> = 0.46
CSF characteristics			
Opening pressure, mm H ₂ O, median (IQR)	30 (19–45)	35 (23–47)	<i>P</i> = 0.48
Initial CSF WBC count/mL median (IQR)	12 (2–65)	10 (2–122)	<i>P</i> > 0.50
India ink positive, n (%)	22 (85)	62 (94)	<i>P</i> = 0.15
Duration of hospitalization, median d (IQR)	20 (17–24)	19 (17–25)	<i>P</i> > 0.5
Death in hospital, n (%)	2 (8)	14 (21)	<i>P</i> = 0.22

GCS, Glasgow Coma Scale.

* Exact methods used.