Toxoplasmosis Encephalitis: A Cross-Sectional Analysis at a U.S. Safety-Net Hospital in the Late cART Era

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Abstract
Despite decreasing incidence of toxoplasmosis encephalitis (TE) among people living with HIV (PLWH) in the late antiretroviral era, U.S. safety-net hospitals still see significant numbers of admissions for TE. Little is known about this population, their healthcare utilization and long-term outcomes. We conducted an 8-year retrospective review of PLWH with TE at a safety-net hospital. Demographics, clinical characteristics, treatments, readmissions, and outcomes were collected. We used chi-squared test to evaluate 6-month all-cause readmission and demographic/clinical characteristics. Of 38 patients identified, 79% and 40% had a new diagnosis of TE and HIV respectively. 59% had 6-month all-cause readmission. Social factors were associated with readmission (uninsured \((p = 0.036)\), Spanish as primary language \((p = 0.017)\), non-adherence \((p = 0.030)\)) and not markers of clinical severity (ICU admission, steroid-use, concomitant infections, therapeutic adverse events). Despite high readmission rates, at follow-up, 60% had a complete response, 30% had a partial response. Improving TE outcomes requires focus on culturally competent, coordinated care.

Keywords
toxoplasmosis encephalitis, HIV/AIDS, readmissions, Latino/Hispanic, health disparities

Introduction
Since 1996 and the advent of combined antiretroviral therapy (cART), the incidence of opportunistic infections (OI) among people living with HIV (PLWH), including toxoplasmosis encephalitis (TE), has dramatically declined.\(^1,2\) A large French cohort study noted the incidence of TE decreased from 3.9 cases/100 person-years pre-cART (1992-1995) to 1 case/100 person-years in the era immediately after cART was introduced (1996-1998).\(^3\) Furthermore, with timely institution of TE therapy and cART, morbidity and mortality among patients with AIDS-related TE has also declined.\(^4,5\) A U.S. study utilizing the national inpatient sample dataset identified a peak of TE-related hospitalizations in 1995 at 10,583 which has since progressively declined reaching the lowest rates in 2001 at 3643 hospitalizations.\(^2\) However, despite advances in diagnosis of HIV and TE and the widespread use of more potent cART, since 2001, the rates of TE-related hospitalization have not declined further.

Even in high income countries, like the U.S., where cART is widely available, there continue to be certain groups of PLWH who still develop TE in the setting of AIDS. TE may occur in PLWH who are diagnosed late in the course of HIV infection or in individuals who were previously diagnosed but not engaged in HIV care or taking cART. Oftentimes, these groups include racial minorities and are localized in areas of the Southern US where urban, safety-net hospitals continue to care for patients with advanced AIDS and OIs.\(^6\)

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What Do We Already Know about This Topic?
In the early years after the advent of combination antiretroviral therapy (cART) in 1996, the number of Toxoplasmosis Encephalitis (TE) hospitalizations in the U.S. dramatically declined; however, since 2001, despite continued advances in cART and other diagnostic and therapeutic interventions, hospitalizations for TE still remain significant in certain parts of the U.S. Although there are a number of studies of TE patients in settings outside the U.S. in the post-cART era, there is limited published data on the U.S. HIV patients who are still getting hospitalized and readmitted for TE in this post-cART era.

How Does Your Research Contribute to the Field?
Our research examines a more contemporaneous and U.S. focused cohort of patients hospitalized for TE in order to understand their clinical characteristics, outcomes and their risk factors for readmission. Our research shows that socio-behavioral factors (lack of insurance, Hispanic ethnicity, Spanish as the primary language and non-adherence to treatment) are more important risk factors for 6 months readmission than traditional clinical factors of disease severity at presentation.

What Are Your Research’s Implications toward Theory, Practice, or Policy?
The post-discharge period may be a highly vulnerable period after TE hospitalization, particularly for uninsured, non-English speaking, Hispanic patients who may struggle with medication adherence. In order to reduce readmissions amongst TE patients, interventions should focus on improving the quality of post discharge care including ensuring culturally appropriate instructions, focus on medication adherence, patient navigation and linkage to care.

Several studies outside of the US (Europe and Brazil) have focused on differences in TE incidence, presentation and outcomes between the pre-and post-cART eras. However, there are limited published data on the experience of patients with AIDS related TE in the US in this post-cART era. More contemporary and regionally-relevant data is needed regarding the characteristics of this patient population, their health care utilization and long-term outcomes in order to provide relevant interventions to improve outcomes.

In this study, we seek to: (a) describe the clinical characteristics and outcomes for PLWH diagnosed with TE in the late cART era in a large safety net hospital system in the southern U.S. and (b) determine factors associated with hospital readmission, a key quality metric. The overarching goal of this project is to identify opportunities to improve the quality of care and clinical outcomes in this vulnerable population.

Methods
Design and Setting
We conducted a detailed retrospective electronic health record review of all cases of probable and proven TE among individuals with HIV admitted to Parkland Health & Hospital System (PHHS) in Dallas, TX from 1/1/2009 (the year the electronic health record system was fully implemented)-4/30/2017. PHHS is a large 862 bed safety-net hospital that provides care to residents of Dallas County, including a large number of uninsured and underinsured patients. PHHS also has an associated outpatient HIV program that serves greater than 6000 PLWH annually.

Data Source and Variables
All patients with an HIV diagnosis (ICD 9 of 042 or V08 or ICD 10 codes B20 or Z21, or HIV listed on their problem list) and a diagnosis of TE (ICD 9 code of 130 or ICD 10 of B58, or Toxoplasmosis listed on their problem list) were included. Electronic health records were manually reviewed by medical physicians trained in infectious diseases. A proven case of TE was defined as: (1) a compatible clinical syndrome; (2) identification of one or more mass lesions by brain imaging; and (3) detection of the organism in a biopsy specimen. A diagnosis of TE was considered probable if the patient: (1) had a compatible clinical syndrome; (2) brain imaging that demonstrates a typical radiographic appearance; and (3) an objective clinical and radiologic response to T. gondii therapy in the absence of a likely alternative diagnosis. Patients were included if they had an HIV diagnosis and proven or probable TE diagnosis and were hospitalized in PHHS between 1/1/2009 and 4/30/2017. We excluded patients who were less than 18 years of age, who were HIV uninfected, who did not meet criteria for proven or probable diagnosis of TE and those who reported a history of TE during the index hospitalization but did not have active disease.

For those patients who met inclusion criteria, we collected data on: demographics (age, race and ethnicity, gender, primary language, insurance, history of mental health diagnosis, history of substance or alcohol use or misuse, and housing instability), baseline HIV characteristics (risk factors for HIV, date of HIV diagnosis, history of ART, OI and prophylaxis treatment prior to index hospitalization, CD4 cell count and HIV viral load (VL)), presenting clinical symptoms, CSF findings, and MRI characteristics (single vs multiple lesions, contrast enhancement, presence of midline shift). We also collected data from the index hospitalization on disease severity or complexity including admission to an intensive care unit, neurosurgical intervention, use of adjunctive steroids,
concomitant OI diagnosis or need to change TE therapy as a result of an adverse event to therapy.

**Longitudinal Data**

We obtained data on clinical response at first outpatient follow up visit, at 6 months, 12 months, and last follow-up from index admission date. Clinical response was coded as complete response, partial response, no response or progression of disease based on medical provider documentation at the time of evaluation. We also collected information on retention in care (based on the CDC definition of at least 2 CD4 cell counts or viral load tests performed at least 3 months apart during the year of evaluation), treatment adherence (defined by the patients’ clinic provider at first outpatient visit), laboratory outcomes at 6 months and 12 months (CD4 and VL) and dates and numbers of readmissions, which were characterized as secondary to relapsed TE or not.

**Analysis**

The primary outcome evaluated was number of all-cause readmissions within 6 months after initial toxoplasmosis admission. We defined the index date as the date of TE admission and defined demographic and clinical characteristics on that index date of admission. We used descriptive statistics to determine the association between 6 month all-cause readmission and baseline demographics, clinical characteristics and early follow up parameters (adherence, time to first outpatient appointment, time to initiation of cART). The secondary outcome evaluated was long term clinical response (at 6 months, 12 months and last follow up).

**Results**

203 unique patients were identified from the electronic medical records with ICD codes for both HIV and Toxoplasmosis. Of those, 57 patients were associated with an inpatient encounter at PHHS during the study period and of those, 38 patients had active TE during their admission.

**Patient Demographics**

Among the 38 patients who fulfilled the inclusion criteria (Table 1), there were 130.9 person-years total follow up time (median 2.95 years, range 0.06-9.67 years). The majority (79%) of these patients presented with a new diagnosis of TE; 21% presented with a relapse of previously diagnosed TE during index hospitalization. 55% were male, 74% were Hispanic and the median age at index date was 39 years. Spanish was the primary language spoken by 71% and 66% were uninsured. HIV diagnosis occurred at time of TE diagnosis in 40%.

**Clinical Characteristics at Index Hospitalization**

During the index hospitalization (Table 2), 32% had midline shift on imaging, 61% required adjunctive steroids, 37% required an ICU admission, and 38% were diagnosed with a concomitant OI. Pyrimethamine + sulfadiazine for induction was initiated on 76%. Fifty-one percent (19/37) of patients had an adverse reaction to TE treatment, of which 79% (15/19) required a change in therapy.

**Longitudinal Follow-Up**

At first outpatient follow up appointment (median 31 days, range 8-192 days) (Table 3), 68% (23/34) were adherent, 18% (6/34) were partially-adherent and 16% (5/34) were non-adherent with TE therapy. Initiation of cART occurred at a median of 34 days (range of 2-1850) after starting toxoplasmosis therapy. At first follow up, 6 months and 12 months, median CD4 count (cells/μL) was 49, 116 and 162 respectively and the percentage of patients with a VL <200 copies/mL was 23%, 56% and 62% respectively. The majority (87%) were retained in care during the first year of follow up.
At 6 months, 47% (14/30) had a complete response (CR) and 27% (8/30) had a partial response (PR). At last follow up (median 2.95 years, range 0.06-9.67 years), 60% (22/37) had a CR and 30% (11/37) had a PR; 8% (3/37) had disease progression and 19% (7/37) had persistent focal neurologic deficit.

During follow up, there were 3 deaths (2 related to TE, 1 from cirrhosis).

Readmissions

Over half, 20/34 (59%), had at least one all-cause readmission during 6 months of follow up with 41 total readmissions (Table 4). Factors associated with readmission included lack of insurance (p = 0.036), Spanish as the primary language (p = 0.017), nonadherence to treatment (p = 0.030) and first episode of TE on admission (p = 0.042). ICU admission, need for adjunctive steroids, midline shift on imaging, concomitant diagnosis of OI, need to change therapy as a result of adverse events and time to outpatient follow up and time to initiation of cART were not associated with 6 months all-cause readmission. Readmission for relapsed TE occurred in 40% (15/38 patients with 39 readmissions) with a median time of 6.9 months, of which 80% (12/15) and 71% (10/14) were non-adherent with TE treatment and cART respectively.

Discussion

Within a high-income country during the late cART era in our safety net hospital institution, we identified 38 unique patients between 2009-2017 with at least one admission for active TE. Of this group, 59% had at least 1 all-cause readmission within 6 months, including 40% with ≥ 1 readmission for relapsed TE during the follow up period. Despite significant markers of disease severity and complexity during index admission, we found that the most common risk factors for 6-month all-cause readmission were not clinical characteristics (presence of midline shift, ICU admission, concomitant OI diagnosis, and adverse effect to TE therapy) but were instead socio-behavioral factors (lack of insurance, being of Hispanic ethnicity, Spanish as the primary language and non-adherence to treatment). Nevertheless, in the long term most patients did well clinically. At 6 months and at last follow up, 47% and 60% obtained a CR and 27% and 30% obtained a PR respectively. In addition, 87% of all patients were retained in care and 61% achieved virologic suppression within a year.

Although the absolute number of patients identified in our single institution is relatively small, in striking comparison, a recent study using the Denmark registry identified 40 patients with TE within the entire country during a study period twice as long (1997-2014). This suggests that PHHS and other safety net

Table 2. Presenting Clinical Symptoms, Laboratory, Radiologic Results and Concomitant OI Diagnosis of TE Patients at Index Hospitalization.

| Clinical presentation | Proportion % |
|-----------------------|--------------|
| Headache              | 22/34 (67.6%)|
| Focal neurologic symptoms | 24/38 (63.2%)|
| Cognitive impairment  | 14/33 (42.4%)|
| Seizures              | 13/36 (36.1%)|
| Fever                 | 12/35 (35.3%)|
| Altered consciousness | 10/37 (27%)  |
| Meningal symptoms     | 0/36 (0%)    |
| Toxoplasmosis IgG+    | 36/37 (97.3%)|
| Lumbar Puncture performed | 28/38 (73.7%)|
| Toxoplasmosis PCR+    | 8/26 (30.8%) |
| CSF pleocytosis (>10 cells) | 8/28 (28.6%)|
| Abnormal protein (>45 mg/dl) | 13/28 (46.4%)|
| Abnormal glucose (<40 mg/dl) | 2/28 (7.1%) |
| Number of MRI lesions |              |
| 1                     | 13/38 (34.2%)|
| 2-5                   | 9/38 (23.7%) |
| >5                    | 16/38 (42.1%)|
| Contrast Enhancement on MRI | 38/38 (100%)|
| Mass Effect           | 24/38 (63.2%)|
| Midline Shift         | 12/38 (31.6%)|
| Need for Neurosurgical Intervention | 5/36 (13.9%)|
| Admission to intensive care unit | 14/38 (36.8%)|
| Concomitant opportunistic infections diagnosed during hospitalization | 14/37 (37.8%)|
| candidiasis           | 7/37 (18.9%) |
| cytomegalovirus (CMV) disease | 6/37 (16.2%)|
| bacterial infection   | 2/37 (5.4%)  |
| non-tuberculosis mycobacteria, disseminated or extrapulmonary | 2/37 (5.4%)|
| herpes simplex virus, bronchitis, pneumonitis, esophagitis | 2/37 (5.4%)|
| disseminated histoplasmosis | 1/37 (2.7%)|
| central nervous system lymphoma | 1/37 (2.7%)|
| HIV wasting syndrome  | 1/37 (2.7%)  |

Table 3. Longitudinal Clinical Outcomes.

| Clinical response | First follow up* (N = 33) | 6 Months (N = 30) | 12 Months (N = 24) | Last known follow up** (N = 37) |
|-------------------|----------------------------|-------------------|-------------------|-------------------------------|
| Complete response | 11 (30.3%)                 | 14 (46.7%)        | 14 (58.3%)        | 22 (59.5%)                    |
| Partial response  | 18 (54.5%)                 | 8 (26.7%)         | 4 (16.7%)         | 11 (29.7%)                    |
| No change         | 2 (6.1%)                   | 3 (10%)           | 1 (4.2%)          | 1 (2.9%)                      |
| Progression       | 2 (6.1%)                   | 5 (16.7%)         | 5 (20.8%)         | 3 (8.1%)                      |

*Median time to first follow up: 31 days (range 8-192 days).

**Median time to last known follow up: 1075 days (range 22-3529).
hospital in the South are taking care of a disproportionately high number of patients with advanced AIDS and TE compared to other high-income countries. While the baseline clinical characteristics of our study population (45% cART naïve, median CD4 37, 40% newly diagnosed with HIV at time of TE diagnosis) were similar to other studies done in high and upper middle income countries, the demographics of our patients differed significantly (74% Hispanic, 71% spoke Spanish as a primary, 66% were uninsured). Some of these demographic differences were also found to be risk factors for readmission.

Though PHHS does serve a large Hispanic population, in a recent study examining the use of a model to predict readmission of hospitalized PLWH in this same institution only 16% were Hispanic; thus the disproportionately high numbers of Hispanic patients among our TE patients cannot be fully explained by the patient population as a whole. As other studies have noted, a higher proportion of TE in Hispanics is expected given a higher baseline toxoplasma seroprevalence among individuals born in Central and South America. The National Health and Nutrition Examination Survey from 1999-2004 reported that the seroprevalence of Toxoplasmosis among Mexican Americans was 13.7% compared with 8.7% of whites. In addition to a higher baseline seroprevalence of toxoplasmosis, other studies have noted that Hispanics are more likely than other ethnic groups to be diagnosed with HIV late (late diagnosis were found in 46% Hispanics, 42% Blacks and 28% White), putting them at higher risk of presenting with AIDS-defining illnesses such as TE.

Readmissions data have often been used to understand efficiency and quality of care. In our study, all cause readmission at 6 months was 59%. This was significantly higher than even the 1 year all cause readmission rate in large cohort studies of PLWH in New York (27.5%) and Pennsylvania (58%). U.S. studies examining readmission in PLWH have noted that social factors (insurance status, unstable housing, substance use) in addition to clinical factors (having an AIDS defining illness, psychiatric and multiple comorbid conditions) are risk factors for readmission. While all TE patients in our study by definition had an AIDS defining illness, which partly explains the higher rate of readmission, additional social variables may also be contributing. We had hypothesized that markers of disease severity or complications during hospitalization (i.e., midline shift, ICU admission, need for steroids, adverse events associated with TE medications) would be associated with increased risk for 6 month all-cause readmission. However, in our analysis, we found the risk factors for all cause readmission centered around social, not clinical issues.

While others US studies have noted the impact of insurance on readmission, most studies found that Medicaid insured patients were more likely to have readmissions compared with Medicare and commercial insurance; of note, in these studies, the uninsured only accounted for about 3.4%-5%. In contrast, the baseline uninsured rate was 66% in our patients and was positively associated with risk of readmission.

Our data is consistent with other studies that have also found that non-English speakers had higher rates of readmission compared with English speaking patients. In one study, Chinese and Spanish speakers were 70% more likely to have a 30 day readmission compared with English speakers. In another study, patients with limited English proficiency were 30% more likely to have a return visit to the emergency department resulting in admission compared with patients with English proficiency. Similarly in our study, we found that patients who spoke Spanish as their primary language had a higher proportion of 6 months all cause readmissions.

Table 4. Association Between Demographic, Social and Clinical Characteristics and 6-Month All Cause Readmission.

| Risk factors                                | No readmission N = 14 (%) | ≥1 Readmission N = 20 (%) | P  |
|---------------------------------------------|---------------------------|---------------------------|----|
| Male                                       | 9 (64.3%)                 | 10 (50%)                  | 0.41|
| Uninsured                                  | 6 (42.9%)                 | 16 (80%)                  | 0.03|
| Spanish as Primary Language                | 7 (50%)                   | 18 (90%)                  | 0.01|
| Hispanic                                   | 8 (57.1%)                 | 18 (90%)                  | 0.03|
| History of substance abuse                 | 4 (28.6%)                 | 1 (5%)                    | 0.06|
| History of mental health                   | 5 (35.7%)                 | 2 (10%)                   | 0.8 |
| First episode toxoplasmosis               | 8 (57.1%)                 | 18 (90%)                  | 0.03|
| Compliance with toxoplasmosis treatment    | 12 (85.7%)                | 9 (45%)                   | 0.02|
| intensive care unit admission              | 6 (42.9%)                 | 6 (30%)                   | 0.44|
| Steroids                                   | 8 (57%)                   | 12 (60%)                  | 0.73|
| Midline shift on initial MRI               | 3 (21.4%)                 | 8 (40%)                   | 0.25|
| Concomitant opportunistic infection         | 11 (78.6%)                | 10 (50%)                  | 0.09|
| Need to change toxoplasmosis therapy       | 10 (71.4%)                | 10 (50%)                  | 0.21|
| Mean time to 1st follow up (SD*)           | 35 (17.9)                 | 43 (45.3)                 | 0.52|
| Median CD4 cell count (µL) at baseline (SD*)| 59.5 (42.2)              | 36.7 (30.6)               | 0.12|
| Median CD4 cell count (µL) at 6 months (SD*)| 177.6 (82)               | 114.6 (85.2)              | 0.06|
| Median Time (days) to HAART initiation (SD*)| 32.2 (19.2)              | 216.7 (524.8)             | 0.2 |

*SD = standard deviation.
Studies in the late cART era\textsuperscript{5,15} noted 1 year relapse rates between 4\%-11.1\%, which were associated with nonadherence to secondary prophylaxis. In contrast, in our study, 40\% of patient were readmitted for relapsed TE during a median follow up period of 3 years, of which 86\% of these patients were nonadherent with TE treatment. This high rate of nonadherence, which may be related to the insurance and language barriers noted above, likely contribute to the fact that while the rates of TE hospitalizations have declined significantly between 2003-2008, the rate of TE hospitalizations remains high among Hispanic patients.\textsuperscript{2}

Despite these repeat admissions, in the long term, similar to other studies, we found that most patients actually improved clinically. The Danish Cohort study noted 3 months after TE diagnosis, morbidity and mortality declined to minimal levels.\textsuperscript{1}

In our study, 60\% of patients obtained a complete response and 30\% partial response at median follow up period of 2.9 years, which is higher than other studies such as the Danish cohort study (30\% of patients had CR, 46\% had a PR at 3 years)\textsuperscript{1} and the Brazilian study (25\% had CR and 38\% had PR at 1 year).\textsuperscript{5} This discordance between high rates of readmission and relapse and improved long term outcomes can be explained by 2 possible factors. One is from the timing of cART itself; studies looking at the effect of cART consistently show a more pronounced effect of cART after the first year with progressive time-dependent reduction in risk during the first 2-3 year of cART.\textsuperscript{11,17} We suspect that the second factor is that once patients are able to overcome short-term barriers related to a new diagnosis, lack of insurance, or difficulties navigating the health care system; long-term adherence was sustained and translated to improved long-term outcome. In our study, 87\% of all patients were retained in care during the first year after index hospitalization and 61\% of all patients were virologically suppressed within a year. In comparison, the CDC National HIV Surveillance System reported that in 2014, 58.3\% and 58.2\% of Hispanics were retained in care and virally suppressed.\textsuperscript{18}

The strengths of this study include a long follow up time with a relatively large number of patients with TE. However, there are several limitations to this study. This study was a single-site safety-net hospital retrospective chart review. The overall cohort, though comparable to other published cohorts, was relatively small, limiting results to descriptive and univariate analyses. Also, our site was located in the southern US, which may limit generalizability of our data, though our patient population is likely comparable to other safety-net hospitals in large urban centers in the South. There was no standardized scoring system to assess clinical improvement or deterioration; rather, clinician reviewers determined patients clinical and neurologic status based on the review of providers’ charting assessment, which may have underestimated the degree of ongoing neurologic involvement. Furthermore, as follow-up data were limited to PHHS, admissions at outside facilities were not accounted for in our dataset, which may underestimate overall readmissions in our cohort.

In conclusion, despite the known efficacy of TE therapy and newer and more potent cART, TE still remains an important cause of morbidity in this modern cART era in high income countries, particularly among Hispanics. Our findings highlight that TE patients are unique compared with the overall population of hospitalized PLWH and may have different needs compared with their counterpart. In addition, our findings underscore that the post discharge period may be a highly vulnerable period after TE hospitalization particularly for uninsured, non-English speaking patients. This group may benefit from culturally appropriate, tailored interventions that address medication adherence, include culturally appropriate discharge instructions, patient navigation and linkage to care in order to improve short term morbidity and unnecessary hospital utilization.

Authors’ Note

Our study did not require an ethical board approval because it did not contain human or animal trials

Declaration of Conflicting Interests

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