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Central Nervous System Disorders after Starting Antiretroviral Therapy in South Africa

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Abstract

Objective—To describe the spectrum of central nervous system (CNS) disease during the first year of antiretroviral therapy (ART), and to determine the contribution of neurological immune reconstitution inflammatory syndrome (IRIS).

Design—A prospective observational cohort study conducted over a 12-month period at a public sector referral hospital in South Africa.

Methods—HIV seropositive patients who developed new or recurrent neurological or psychiatric symptom(s) or sign(s) within the first year of starting ART were enrolled. We used the number of patients starting ART in the referral area in the preceding year as the denominator to calculate the incidence of referral for neurological deterioration. Patients with delirium and peripheral neuropathy were excluded. Outcome at six months was recorded.

Results—Seventy-five patients were enrolled. The median nadir CD4+ count was 64 cells/ μ L. 59% of patients were receiving antituberculosis treatment. The incidence of referral for CNS deterioration in the first year of ART was 23.3 cases (95% CI, 18.3–29.2) per 1000 patient years at risk. CNS tuberculosis (n=27, 36%), cryptococcal meningitis (n=18, 24%), intracerebral space occupying lesions (other than tuberculoma) (n=10, 13%) and psychosis (n=9, 12%) were the most frequent diagnoses. Paradoxical neurological IRIS was diagnosed in 21 patients (28%), related to tuberculosis in 16 and cryptococcosis in 5. At 6 months, 23% of patients had died and 20% were lost to follow-up.

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Conflicts of interest

We declare no conflict of interest.

Conclusion—Opportunistic infections, notably tuberculosis and cryptococcosis, were the most frequent causes for neurological deterioration after starting ART. Neurological IRIS occurred in over a quarter of patients.

Keywords

HIV; Neurological Disorders; Central Nervous System Diseases; Immune Reconstitution Inflammatory Syndrome; Antiretroviral Therapy

INTRODUCTION

Neurological disorders are important causes of morbidity and mortality in human immunodeficiency virus (HIV)-infected patients [1,2]. The use of combination antiretroviral therapy (ART) has significantly reduced the incidence and progression of HIV-associated dementia (HAD), as well as the incidence of opportunistic infections affecting the central nervous system (CNS) [3]. However, an early complication of ART is the immune reconstitution inflammatory syndrome (IRIS), which may affect the CNS [4,5]. IRIS occurs due to an exuberant inflammatory response directed towards opportunistic pathogens [6]. This results in the paradoxical worsening of a patient's condition despite adequate antimicrobial therapy (paradoxical IRIS), or the unmasking of an occult opportunistic infection with an unusually inflammatory presentation (unmasking IRIS) [7]. Neurological IRIS is described in several HIV-related CNS disorders, such as tuberculosis (TB), cryptococcal meningitis (CM), cytomegalovirus infection, and progressive multifocal leukoencephalopathy [4,5].

Efavirenz (EFV) may cause CNS adverse events in more than 50% of patients [8,9]. Furthermore, a Thai study reported an increased rate of primary CNS lymphoma and ischemic/hemorrhagic strokes in HIV-infected patients within the first two years of ART when compared to HIV-infected patients from the same setting in the pre-ART era [2].

In this study, we describe the spectrum of CNS disease during the first year of ART among patients presenting to a referral hospital in South Africa.

METHODS

A prospective observational study at GF Jooste Hospital, a secondary-level, public sector referral hospital in Cape Town, South Africa. GF Jooste Hospital serves adults from a population of approximately 1.3 million people who reside in high-density, low-income communities. The incidence of TB in these communities exceeds 1,000 cases per 100,000 of the population per annum and the antenatal HIV seroprevalence can be 30% [10]. Eleven primary-level ART clinics are situated in the referral area. Most patients attending these clinics do not have health insurance. Thus the public sector referral hospital serves most patients with significant clinical deterioration following ART initiation.

Between 1 November 2007- 31 October 2008 (12 months), we enrolled adult (>18 years of age) HIV seropositive patients who were referred to our facility with new or recurrent neurological or psychiatric symptom(s) or sign(s) within the first year of starting ART. Patients with neurological deterioration due to peripheral neuropathy or 'delirium secondary to a general medical condition' were excluded. Doctors in the infectious diseases outpatient clinic, and the admitting medical doctors were informed about the study and screened all patients who presented to GF Jooste hospital with a medical illness. Patients who met the inclusion criteria were referred to a study physician. The study physicians also actively sort out referrals in the outpatient clinic and medical wards each day of the week (Monday to Friday). Data obtained by the study physician included demographic information, CD4⁺

count prior to ART initiation, ART regimen, previous/concurrent illnesses affecting the CNS, details of TB disease if present, medication use and details of neurological presentation. Thereafter, a neurological examination was performed by the study physician and investigations requested as determined by presentation. We subsequently used primary clinic and hospital medical notes, as well as the National Health Laboratories Service database to trace specimens, and the electronic hospital and primary clinic attendance registers to trace patients, in order to determine the outcome six months after presentation. Data obtained prospectively (i.e. details regarding presentation and initial management) as well as retrospectively (i.e. outcome data), were recorded on a standardized data collection sheet. Data analysis was performed using Microsoft Excel. The incidence of referral for CNS deterioration was calculated with 95% Poisson confidence intervals (CI) based on the total number of patients initiating ART in the year preceding each study month at the 11 referring ART clinics, reduced by 10.9% to allow for losses to care. The data were obtained from monthly reports of total patients started on ART in each referring clinic and provincial cohort data on retention in care at six months on ART [11]. The Research Ethics Committee of the University of Cape Town approved this study.

Definitions

We defined paradoxical TB-IRIS and CM-IRIS using consensus clinical case definitions [7, 12, 13]. The diagnosis of **paradoxical TB-IRIS** required 1) diagnosis of active TB prior to ART initiation, 2) response to antitubercular treatment and, 3) development of recurrent, new or worsening symptoms/signs of neurological TB within three months of starting ART. Paradoxical TB-IRIS was also diagnosed in patients who 1) were diagnosed with TB *after* initiation of ART and, 2) subsequently, developed a neurological paradoxical reaction after starting antitubercular therapy, 3) that did not have an alternative explanation. The diagnosis of **paradoxical CM-IRIS** required 1) diagnosis of CM prior to ART, 2) initial response to antifungal treatment with improvement of symptoms/signs and, 3) presentation with CM recurrence that was culture negative within 12 months of ART initiation. If there was a CM recurrence on ART and the CSF cultured *Cryptococcus neoformans*, the onset of the event had to be within three months of initiation of antifungal therapy to be defined as CM-IRIS. The diagnosis of **a culture positive CM relapse on ART** required 1) re-presentation with CSF fungal culture positive CM and, 2) occurrence more than three months after start of antifungal therapy. The diagnosis of **'delirium secondary to a general medical condition'** required acute confusion secondary to, 1) sepsis due to a non-neurological infection or, 2) metabolic abnormality (e.g. hypoxia, hypoglycemia, renal or hepatic failure).

RESULTS

Seventy-five patients presented with neurological deterioration within one year of starting ART. Between 1 November 2006 through 31 October 2007, the estimated person time at risk in the first year of ART was 3222 patient years (PY), accounting for losses to care. The incidence rate of referred cases with CNS deterioration in the first year on ART was therefore 23.3 cases (95% CI, 18.3–29.2) per 1000 PY at risk.

Table 1 summarises the 75 patients' clinical and demographic characteristics. Forty-four patients (59%) were receiving antituberculosis treatment at the time of neurological deterioration, 30 of whom had culture-confirmed disease. Drug susceptibility testing for rifampicin and isoniazid (INH) was performed on 18 isolates and revealed drug-susceptibility in 15 cases, and multidrug-resistance (resistant to rifampicin and INH) in three cases. The four most frequent reasons for neurological deterioration were: CNS tuberculosis, CM, intracerebral space occupying lesions (SOL) and psychosis (Table 2).

CNS tuberculosis

Twenty-seven patients (36%) presented with neurological deterioration related to TB. Paradoxical TB-IRIS was diagnosed in 16/75 patients (21%). 13/16 of these patients received corticosteroids. At 6-months follow-up, 15/16 patients were alive, and one was lost to follow-up. All patients diagnosed with tuberculoma either had a negative serum Immunoglobulin G (IgG) serological analysis for *Toxoplasma* species, or showed a good response to antitubercular treatment in the absence of treatment for toxoplasmosis.

Cryptococcal meningitis

Eighteen patients (24%) presented with deterioration related to CM. Five patients (7%) presented with paradoxical CM-IRIS, of whom one received corticosteroids. At six months follow-up, four of these five patients were alive, and one was lost to follow-up.

Space occupying lesions (other than tuberculoma)

Ten patients (13%) presented with SOL due to toxoplasmosis (n=1) or of uncertain aetiology (n=9). The diagnosis of cerebral toxoplasmosis was based on a response to antitoxoplasma treatment in the absence of antitubercular treatment. In the other nine patients it could not be ascertained whether the SOL was related to TB or toxoplasmosis: four were already receiving antitubercular treatment and had antitoxoplasma treatment added, three were started on treatment for both TB and toxoplasmosis, one was treated only for toxoplasmosis but died, and one was only treated for TB but died.

Psychosis

Nine patients (12%) presented with psychosis. An EFV-induced psychosis was the most likely cause in five. One patient was diagnosed with INH-induced psychosis and another was diagnosed with a reactive psychosis secondary to social stressors. A diagnosis of HIV-induced psychosis was presumed for two patients in whom no other cause could be identified.

Outcomes

At six months follow-up, 43 (57%) patients were alive, 17 (23%) were dead and 15 (20%) were lost to follow-up from the health care system (Table 1). The median interval from ART initiation, and presentation, to death was 67 days (IQR 47–164 days) and 23 days (IQR 10–39 days), respectively.

DISCUSSION

This is, to our knowledge, the first prospective study describing the spectrum of neurological disorders occurring within the first year of ART. TB and CM together accounted for at least 60% of cases. This is likely due to the high incidence of TB in our setting, and profound immunosuppression at ART initiation; in 2007, 19% of adults starting ART in the Western Cape Province had a CD4⁺ count below 50 cells/ μ l, while the median CD4⁺ count of patients starting ART in two of the referring clinics was 131 cells/ μ l [14].

Paradoxical IRIS, which was associated with TB (n=16) and CM (n=5), accounted for 28% of cases. Paradoxical CM-IRIS may occur in up to 30% of patients following ART initiation [15–17]. We previously reported neurological TB-IRIS in 12% of patients who presented with TB-IRIS [12]. The median interval from starting ART to symptom onset in our patients with TB-IRIS, and CM-IRIS, was 16 and 58 days, respectively. These findings are similar to previous reports [12,15]. The management of neurological IRIS is problematic; no diagnostic test exists and treatment strategies are based on anecdotal case reports [18]. 81%

of patients with TB-IRIS and 20% of patients with CM-IRIS in our cohort received corticosteroid therapy, which may be of benefit in patients with neurological TB-IRIS [12,18]. High mortality rates have been associated with both CM-IRIS (up to 66%) [17] and neurological TB-IRIS (at least 13%, at 6-months follow-up) [12]. No patients in our cohort who presented with IRIS died during six months follow-up, and only one patient with TB-IRIS, and one with CM-IRIS, was lost to follow-up at six months.

New or expanding SOL developed in 21% of patients (n=16). Confirming the aetiology of SOL is difficult in our setting where access to stereotactic brain biopsy is limited. Similar to previous studies [12], we relied on available evidence to make the diagnosis. The major differential diagnoses of SOL are cerebral toxoplasmosis (diagnosed in one patient) and tuberculoma (diagnosed in six patients) [19]. In more than half of our patients (9/16), the diagnosis was uncertain. The lack of definitive diagnosis in most cases, and the associated high mortality in these cases (6/9), emphasize the challenge of managing patients with SOL.

Neurological deterioration is an important cause of clinical deterioration and death after starting ART. The referral rate of 23.3 cases per 1000 PY at risk is most likely an underestimate of the true incidence of neurological deterioration. Whilst significant neurological presentation related to a CNS cause results in referral to our facility, patients with mild symptoms or signs are not always referred; secondly, patients who are too confused or otherwise unwell to seek medical help may die at home; and thirdly, patients may attend other hospitals or move out of the referral area. Furthermore, new or worsening peripheral neuropathy is a common cause for neurological deterioration after starting ART [20]. However, as most peripheral neuropathies are managed at primary care level, we did not include these patients in our study. In this study, the challenges posed by the management of patients with neurological deterioration are reflected in poor outcome (23% died), and high rate of loss to follow-up (20%), at six months. In comparison, among all patients starting ART in our setting, mortality and loss to follow-up is considerably lower. The cumulative mortality rate during the first year of ART (from 2004 to 2007 in the largest ART clinics in our referral area) was 8%, and 3 - 5 % of patients were lost follow-up during the first year of ART [21]. In a busy ART program, clinic attendance and adherence to ART require patient mobility, insight and motivation. Neurological deterioration makes this difficult, especially if there is inadequate treatment support from family or friends. Patients with psychosis or confusion may not have the insight to seek medical help and may default ART and other medical therapies. Furthermore, patients with weakness or other neurological impairment may be physically incapable of seeking medical care independently. This may contribute to the high loss to follow-up rate we observed.

Conclusion

In our setting, opportunistic infections, notably TB and cryptococcosis, were the most important causes for neurological deterioration during the first year of ART. Over a quarter of cases were related to paradoxical IRIS. Our study has particular relevance to ART programs in high TB prevalence regions. We highlight the challenges associated with the management of these in patients in resource-constrained settings.

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Table 1

Characteristics and outcomes of 75 HIV seropositive patients presenting with neurological deterioration within one year of initiating ART

Female, n (%)	40	(53)
Age in years, median (range)	33	(18–68)
Nadir CD4 ⁺ count, cells/ μ L, median (IQR)	64	(23–114)
WHO Staging, n (%)		
Stage II	2	(3)
Stage III	28	(37)
Stage IV	45	(60)
ART regimen, n (%)		
d4T/3TC/EFV	50	(67)
d4T/3TC/NVP	14	(19)
AZT/3TC/EFV	6	(8)
AZT/3TC/NVP	4	(5)
TDF/3TC/EFV	1	(1)
Current TB, n (%) ¹	44	(59)
Pulmonary/Extra-pulmonary disease ² , n/n	27/22	
Time from antituberculosis treatment initiation to starting ART in days, median (IQR) ³	56	(34–100)
Previous TB, n (%)	31	(41)
Previous CM, n (%)	11	(15)
Time from ART initiation to symptom onset in days, median (IQR)	23	(9–89)
Paradoxical TB-IRIS, n=16	16	(11–30)
Paradoxical CM-IRIS, n=5	58	(27–88)
Time from symptom onset to presentation in days, median (IQR)	4	(3–14)
Paradoxical TB-IRIS, n=16	4	(3–16)
Paradoxical CM-IRIS, n=5	3	(2–4)
Outcome at 6 months, n (%)		
Alive	43	(57)
Dead ⁴	17	(23)
Lost to follow-up ⁵	15	(20)

Abbreviations: HIV, human immunodeficiency virus; ART, antiretroviral treatment; IQR, interquartile range; WHO, World Health Organization; d4T, stavudine; 3TC, lamivudine; EFV, efavirenz; NVP, nevirapine; AZT, zidovudine; TDF, tenofovir; TB, tuberculosis; CM, cryptococcal meningitis; TB-IRIS, tuberculosis-associated immune reconstitution inflammatory syndrome; CM-IRIS, cryptococcal meningitis immune reconstitution inflammatory syndrome

¹ Includes all patients on antituberculosis treatment at the time of neurological deterioration (those who started prior to ART initiation (n=40), and those who started after ART initiation (n=4)).

²Extra-pulmonary disease sites include: nodal (n=11), central nervous system (n=5), abdominal (n=4), pleural (n=4), pericardial (n=2); In 5 patients, both pulmonary and extra-pulmonary disease were present, in 3 patients more than 1 extra-pulmonary site of disease was present.

³For 40 patients who started antituberculosis treatment prior to ART.

⁴Deaths occurred in the following patient categories: intracerebral space occupying lesion (other than tuberculoma) (n=6), new diagnosis of neurological TB (n=2), poor adherence to antitubercular treatment (n=2), multidrug-resistant TB (n=1), new diagnosis of CM (n=3), cytomegalovirus encephalitis (n=1), HIV encephalopathy (n=2)

⁵Lost to follow-up occurred in the following patient categories: paradoxical TB-IRIS (n=1), multidrug-resistant TB (n=2), poor adherence to antitubercular treatment (n=1), paradoxical CM-IRIS (n=1), culture positive CM relapse on ART (n=1), new diagnosis of CM (n=1), cerebral toxoplasmosis (n=1), intracerebral space occupying lesion of uncertain aetiology (n=1), EFV-induced psychosis (n=2), reactive psychosis (n=1), isolated abducens nerve palsy (n=1), varicella zoster virus radiculopathy (n=1), bacterial meningitis (n=1)

Table 2

Causes of neurological deterioration within one year of ART initiation in 75 HIV seropositive patients

	n	(%)
CNS tuberculosis	27	(36)
Paradoxical TB-IRIS ¹	16	(21)
TB meningitis (n=8)		
Tuberculoma (n=6)		
TB arachnoiditis (n=1)		
TB spinal epidural abscess (n=1)		
New diagnosis of neurological TB	4	(5)
TB meningitis (n=3)		
TB arachnoiditis (n=1)		
MDR-TB	2	(3)
Deterioration due to poor adherence	5	(7)
Cryptococcal meningitis [CSF culture positive ²]	18 [12]	(24)
Paradoxical CM-IRIS ¹	5 [1]	(7)
Culture-positive relapse on ART ¹	4 [4]	(5)
New diagnosis of CM	9 [7]	(12)
Intracerebral space occupying lesion ⁵	10	(13)
Cerebral toxoplasmosis	1	(1)
Uncertain aetiology ⁶	9	(12)
Psychosis	9	(12)
EFV-induced	5	(7)
HIV-induced	2	(3)
INH-induced	1	(1)
Reactive psychosis	1	(1)
Other	11	(15)
Seizure	3	(4)
CMV encephalitis	2	(3)
HIV encephalopathy	2	(3)
Isolated abducens nerve palsy	1	(1)
VZV radiculopathy	1	(1)
Bacterial meningitis	1	(1)
RIND	1	(1)

^{1,3,4} See definitions in the text.² CSF culture positive for *Cryptococcus neoformans* at time of deterioration⁵ Space occupying lesions other than tuberculoma⁶ The most likely differential diagnoses included tuberculoma and toxoplasmosis

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; CNS, central nervous system; TB-IRIS, tuberculosis-associated immune reconstitution inflammatory syndrome; TB, tuberculosis; MDR-TB, multidrug-resistant TB; CSF, cerebrospinal fluid; CM-IRIS, cryptococcal meningitis immune reconstitution inflammatory syndrome; EFV, efavirenz; INH, isoniazid; CMV, cytomegalovirus; VZV, varicella zoster virus; RIND, reversible ischemic neurological deficit