Article

Primary Mania Versus HIV-Related Secondary Mania in Uganda

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Objective: The authors hypothesized that in the majority of HIV-positive patients presenting with mania, the mania is secondary to HIV infection and that its presentation and correlates differ from those of HIV-negative patients with primary mania.

Method: A comparative cross-sectional study was conducted with HIV-negative and HIV-positive patients admitted to psychiatric wards with acute mania. The authors compared the patients' psychiatric, physical, and immunological (CD4 cell counts) and other laboratory parameters. Pairwise comparisons were done for the two groups on a number of variables.

Results: Of 141 patients who presented with acute mania during a 6-month period and were eligible for the study, 61 met criteria for HIV-related secondary mania. Compared with HIV-negative patients with primary mania, they were older, more cognitively impaired less educated, and more likely to be female. Patients in this group had more manic symptoms: they were more irritable, more aggressive, more talkative, and had higher rates of paranoid delusions, visual hallucinations, and auditory hallucinations. More of the HIV-positive secondary mania group had CD4 counts below 350 cells/mm^3.

Conclusions: Primary mania and HIV-related secondary mania are clinically and immunologically distinct. The relation between secondary mania and depressed CD4 counts suggests that in the setting of an HIV/AIDS epidemic in poor countries, secondary mania may be used as an indicator to initiate highly active antiretroviral therapy.

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The HIV/AIDS epidemic constitutes a major public health crisis in the developing countries. Sub-Saharan Africa has just over 10% of the world's population but is home to more than 60% of all people living with HIV—estimated at some 25.8 million. In Uganda, one of the countries hardest hit by the epidemic, an estimated 7% of adults nationwide are living with HIV infection (1). The Ugandan government has launched a variety of prevention programs, and additional support has come from the World Health Organization (WHO); the Global Fund to Fight AIDS, Tuberculosis, and Malaria; and the (U.S.) President's Emergency Plan for AIDS Relief to increase access to highly active antiretroviral therapy (2). However, relatively little attention has been given to the psychiatric manifestations of HIV infection, particularly mania (3).

Mania in a patient with HIV/AIDS may occur as a phase of a coexisting bipolar disorder, or it may be secondary to the direct neuronal effects of HIV infection (4), treatments for HIV infection (5–7), or HIV-related secondary infections of the brain (8). Affected patients appear to present with severe psychopathology (9, 10). In developed countries, prevalence studies have shown that mania secondary to HIV infection is common (11, 12), and it occurs more among individuals with AIDS than among those with HIV infection alone (9, 12). Researchers have previously hypothesized that mania occurring in the early stages of HIV infection may represent bipolar disorder in its manic phase, whereas mania in persons with AIDS is secondary mania linked to the pathophysiology of HIV brain infection (11). The evidence for an etiological association with HIV neuropathy was bolstered by a prospective study of HIV-positive patients with and without mania that demonstrated a protective effect from an antiretroviral agent able to penetrate the central nervous system (13). However, given the small sample sizes used in these studies, any conclusions drawn from them should be considered tentative.

The epidemiology of mania secondary to HIV infection in Uganda and other African countries that have high rates of HIV infection and limited access to highly active antiretroviral therapy remains largely unknown. The case registry at Butabika Hospital, Uganda's only psychiatric referral hospital, shows that the number of patients presenting with first-episode mental illness is increasing, with 2,565 recorded in 1999 and 3,504 in 2005. Although population growth and increased government efforts to raise aware-

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ness about mental disorders could explain this trend, it could also be due to an increase in the number of cases in which a mental disorder occurs secondary to HIV infection. Mania is the most common mental disorder seen at this hospital.

A recent study at the referral hospital (14) revealed a prevalence of HIV infection of 18.4% among patients admitted for the first time with severe mental illness, and almost half of these patients presented with mania. Moreover, the rate of HIV infection among patients presenting with first-episode mental illness was about three times the rate among patients who had previous episodes. In this study, we compared the presentation and correlates of primary mania in HIV-negative patients with those of first-episode secondary mania in HIV-positive patients. We hypothesized that in the majority of HIV-positive patients presenting with mania, it would be mania secondary to HIV infection and that its presentation and correlates would differ from those of HIV-negative patients with primary mania.

Method

Over a 6-month period (October 2004–March 2005), we performed a cross-sectional study of adult patients (18 years of age and older) consecutively admitted with acute mania to the general psychiatric wards of Mulago and Butabika Hospitals. Mulago Hospital is the national referral general hospital and a teaching hospital. Its consultation-liaison psychiatry service was established in 1999 to provide psychiatric services for inpatients, ambulatory patients, and those referred by community medical practitioners. Butabika Hospital is the national referral mental and teaching hospital, and it has general psychiatry wards and forensic wards.

All patients underwent routine standard psychiatric, physical, and laboratory assessments. Patients were excluded if found to have a medical condition other than HIV infection and its complications that could be related to the manic episode. The Alcohol Use Disorders Identification Test (AUDIT) (15) was used to exclude those with alcohol dependence. Patients were also excluded if the clinical assessment indicated that they met DSM-IV criteria for delirium or a substance use disorder or if they were in puerperium. HIV-positive patients who had recurrent episodes of mania, a previous depressive disorder, or a family history of mood disorders were considered to have bipolar disorder in the manic phase and were excluded from the study.

Psychiatrists attached to the wards where patients were admitted used DSM-IV criteria to confirm the diagnosis of mania clinically. Manic symptoms at the time of admission were rated on the Young Mania Rating Scale (YMRS) (16) by research assistants (psychiatric clinical officers) who had received training in the use of this scale. The patients were treated with conventional antipsychotics, and when they had insight into their illness and were stable enough to communicate, research assistants explained the study procedures and asked if they would consent to participate in the study. For those who did not consent, any data collected previously were discarded. Those who gave informed consent were assessed with a pretested standardized sociodemographic questionnaire. Collateral information was obtained from family members and others who knew the patient well. The Mini-Mental State Examination (MMSE) (17) was used to assess for cognitive impairment.

The patients' medical records were reviewed, and their medical diagnoses, test results, and physical examination findings were recorded. HIV serostatus was obtained from medical records or self-report. For patients whose HIV serostatus was unknown, pretest counseling was given, and then HIV serology was done. For HIV-positive patients, HIV infection was staged according to the WHO clinical staging system for HIV/AIDS (18).

Primary mania was diagnosed if a patient met DSM-IV criteria for bipolar disorder in the manic phase and was HIV negative. Secondary mania was diagnosed if the patient was HIV positive and had no clear personal or family history of mood disorders (12). Although the criteria of a close temporal proximity of an organic insult to the brain and the subsequent mania as well as late age of onset are often used in defining secondary mania (19), in the case of HIV-related mania, as Ellen et al. have noted, these criteria cannot always be applied because of the prolonged course of HIV infection and the high rate of infection in relatively young people (12).

Statistical Analysis

Statistical analysis was carried out with SPSS, version 11.5. Frequencies of clinical and demographic variables were computed, and bivariate analyses were conducted to identify demographic and clinical variables that were significantly correlated with first-episode secondary mania in order to control for their contribution in multivariate models. For the bivariate analyses, we used chi-square tests or Fisher's exact test for qualitative variables, independent-sample t tests for continuous variables, and Spearman's rank test for correlation coefficients for cases of two quantitative variables. Variables that had a significant bivariate association with secondary mania were then included in a multivariate logistic regression model.

Results

Overall, 160 patients with acute mania were asked to participate in the study. Of these, 141 (88.1%) gave written consent and 19 (11.9%) declined to participate. Of those who gave consent, 64 (45.4%) were HIV negative and therefore considered to have primary mania, and 77 (54.6%) were HIV positive. In the HIV-positive group, 61 (79.2%) were considered to have first-episode secondary mania because of a lack of any personal or family history of mood disorders. The other 16 HIV-positive patients (20.8%) were considered to have a possible primary mania coexisting with HIV infection because of a personal or family history of mood disorders and hence were excluded from data analysis.

Among the patients with secondary mania, only half had been aware of their HIV status prior to their psychiatric hospitalization. Table 1 and Table 2 summarize demographic and clinical variables, respectively, for the two groups of patients. Table 3 and Table 4 summarize manic symptoms as reported by participants and as rated on the YMRS, respectively, for the two groups. A significant correlation was observed between age and YMRS total score ($r=0.28$, $p=0.031$) among HIV-positive patients with secondary mania but not among HIV-negative patients with primary mania.

Cognitive impairment as indicated by the MMSE was greater in HIV-positive patients with secondary mania

TABLE 1. Sociodemographic Characteristics of 125 Patients Presenting With Primary Mania (N=64) or HIV-Related Secondary Mania (N=61) in Uganda

Characteristic	Primary Mania, HIV-Negative		Secondary Mania, HIV-Positive			
	Mean	SD	Mean	SD	t	p
Age (years)	25.2	7.5	35.2	8.4	–7.8	<0.001
	N	%	N	%	χ^2	p
Gender					10.68	<0.001
Male	29	45.3	11	18		
Female	35	54.7	50	82		
Education					13.41	0.001
Primary education or less	18	28.6	37	60.6		
Some secondary education or more	46	71.4	24	39.4		
Marital status					12.11	<0.001
Married	14	21.9	20	32.8		
Single	48	75	21	34.4		
Widowed	0	0.0	11	18		
Divorced or separated	2	3.1	9	14.8		
Religion					1.87	0.687
Christian	54	84.1	52	85.2		
Muslim	10	15.9	9	14.8		
Number of rooms in patient's home[a]					16.20	0.018
1–2 rooms	39	61	49	80.3		
>2 rooms	25	39	12	19.7		

[a] Number of rooms in a person's home is an indicator of socioeconomic status in Uganda.

TABLE 2. Clinical Characteristics of 125 Patients Presenting With Primary Mania (N=64) or HIV-Related Secondary Mania (N=61) in Uganda

Characteristic	Primary Mania, HIV-Negative		Secondary Mania, HIV-Positive			
	Mean	SD	Mean	SD	t	p
Age at onset of mania (years)	21.2	5.5	35.2	8.4	–8.2	0.001
	N	%	N	%	χ^2	p
Source of referral					3.10	0.43
Relative	37	64.3	27	44.2		
Health unit	20	25.8	26	44.2		
Police	7	9.9	8	11.6		
Manic episode					—	—
First episode	24	39.3	61	100		
Recurrent episode	40	62.5	0	0		
Family history of mood disorders						
Yes	55	87.5	0	0	—	—
No	8	12.5	61	100		
Duration of stay					32.0	<0.001
1–2 weeks	2	3.1	29	46.7		
>2 weeks	62	96.9	32	53.3		
Lost sexual partner to AIDS	1	1.6	29	47.5	36.2	<0.001

than in HIV-negative patients with primary mania (MMSE scores: mean=21, SD=3.8, compared with mean=25.4, SD=2.0; t=–7.1, p=0.001). Using the cutoff points provided by Crum et al. (20), we categorized MMSE scores of 21–24 as indicating mild impairment; 16–20, moderate impairment; and 15 and below, severe impairment. HIV-positive patients with secondary mania were more likely to have MMSE scores of 24 or less (odds ratio=6.4, 95% confidence interval (CI)=2.78–14.92, p=0.001), even after controlling for education status (adjusted odds ratio=5.82, 95% CI=2.4–14, p=0.001). Among the HIV-negative patients with primary mania, 28 (45.2%) had mild cognitive impairment. Among the HIV-positive patients with secondary mania, 39 (61.9%) had mild impairment. Moderate impairment and severe impairment were found exclusively among HIV-positive patients with first-episode secondary mania (N=11, or 17.5%, and N=3, or 4.8%, respectively).

HIV-related symptoms were rated using the WHO criteria for diagnosis of AIDS in an adult in Africa (18). The symptoms most frequently reported by the HIV-positive patients with secondary mania were weight loss of more than 10% (reported by 49 patients, or 80%), unexplained fevers for more than 1 month (47, or 77%), diarrhea on and off for more than 1 month (40, or 65.6%), recurrent skin infections (39, or 63.9%), and having suffered from pulmonary tuberculosis in the past 2 years (27, or 44.3%). However, at the time of presentation, only two HIV-positive patients (3.3%) were febrile and two (3.3%) were jaundiced. Thirty-nine (64%) had fungal infections, 48 (80%) had generalized lymph node enlargement, 40 (66%) had dermatitis, and 10 (16.4%) had peripheral neuropathy. According to the WHO clinical staging system for HIV/AIDS, 11 HIV-positive participants (18%) were in stage 1, 18 (29.5%) in stage 2, 28 (45.9%) in stage 3, and 4 (6.6%) in stage 4.

HIV-positive patients with secondary mania were more likely to be immunologically suppressed (mean CD4 cell count=392 cells/mm^3, median=272, range=6–1,182) than

TABLE 3. Manic Symptoms Reported by 125 Patients Presenting With Primary Mania (N=64) or HIV-Related Secondary Mania (N=61) in Uganda

	Primary Mania, HIV-Negative		Secondary Mania, HIV-Positive			
Symptom	N	%	N	%	χ^2	p
Excessive happiness	57	89.1	22	36.1	36.04	<0.001
Undressing in public	42	65.6	42	68.9	0.25	0.701
Violent and aggressive behavior	59	92.2	60	98.4	2.73	0.107
Possessed by spirits	35	54.7	36	59	0.08	0.625
Paranoid delusions	51	79.7	56	91.8	4.00	0.05
Visual hallucinations	10	15.6	57	93.4	72.61	<0.001
Auditory hallucinations	10	15.6	41	67.2	32.67	<0.001

TABLE 4. Manic Symptoms as Rated with the Young Mania Rating Scale in 125 Patients Presenting With Primary Mania (N=64) or HIV-Related Secondary Mania (N=61) in Uganda

	Primary Mania, HIV-Negative		Secondary Mania, HIV-Positive		
Young Mania Rating Scale Item	Mean	SD	Mean	SD	p
Elevated mood	3.1	1.1	1.0	1.2	<0.001
Excessive motor activity-energy	3.4	0.5	3.8	0.41	0.001
Sexual interest	1.7	0.8	1.4	0.9	0.118
Lack of sleep	3.4	0.5	3.8	0.6	0.01
Irritability	4.1	1.8	7.5	1.2	<0.001
Speech (rate and amount)	5.3	1.3	6.4	1.1	0.019
Language-thought disorder	2.8	0.5	3.1	0.7	0.019
Content	5.7	1.2	7.6	0.9	<0.001
Disruptive-aggressive behavior	5.4	2.0	7.2	1.7	0.001
Appearance	1.5	0.9	1.8	0.9	0.06
Insight	3.8	0.6	3.9	0.4	0.338
Total score	40.2	5.5	48.0	5.5	<0.001

HIV-negative patients with primary mania (mean CD4 count=823 cells/mm^3, median=737, range=340–2,062). Among the HIV-positive patients with secondary mania, 28 (46%) had CD4 counts below 200 cells/mm^3, seven (11.4%) had counts in the range of 201–350 cells/mm^3, four (6.6%) in the range of 351–500 cells/mm^3, and 22 (36.1%) had counts above 500 cells/mm^3. Among HIV-negative patients with primary mania, none had a CD4 count below 200 cells/mm^3, one (1%) was in the range of 201–350 cells/mm^3, six (9.4%) were in the range of 351–500 cells/mm^3, and 57 (89.1%) had counts above 500 cells/mm^3.

In the multivariate logistic regression model, three factors had a significant association with HIV-related secondary mania: age in the range of 30-49 years [odds ratio=4.0, 95% confidence interval (CI)=1.09–14.8, p=0.037]; lost a partner to HIV (odds ratio=9.2, 95% CI=0.79–106.98, p<0.01); and history of a cough for more than 1 month (odds ratio 46.4, 95% CI=5.25-409, p<0.001).

Discussion

The majority of HIV-positive patients with mania met criteria for first-episode secondary mania. Compared with HIV-negative patients with primary mania, they were older, more likely to be female than male (the male-to-female ratio was 1:5), and less likely to have completed secondary school, and hence more were unemployed; as a result, more were of a low socioeconomic status (80% versus 60%). The divorced and separated were more likely to be found among HIV-positive individuals with secondary mania than among the HIV-negative individuals with primary mania. Widows were found exclusively among the HIV-positive patients with secondary mania; indeed, significant number of the HIV-positive study subjects (29, or 47.5%) had lost a spouse or partner to AIDS.

Our findings on sociodemographic characteristics differ from those reported in developed countries, where patients with first-episode secondary mania in HIV infection have been mostly Caucasian males [male-to-female ratios as high as 8:1 have been reported (9–12)] and where majorities had a college education and were not of low socioeconomic status. These differences may be explained by the markedly different geographical, political, socioeconomic, and cultural factors between the developed and developing countries. In Africa, heterosexual transmission of HIV predominates (1). Infected men are more likely to have multiple partners, and hence women are more frequently exposed to the risk of infection, and they acquire the infection more easily and more frequently than males. In sub-Saharan Africa, where most HIV-infected individuals live, women represent 52% of the 25.8 million adults living with HIV infection (1). Interestingly, only 48% of the HIV-positive patients in our study were aware of their HIV status before they developed mania, which suggests that mania itself may prompt initial diagnosis of the infection.

Clinically, compared with HIV-negative patients with primary mania, HIV-positive patients with first-episode secondary mania had more manic symptoms, according to the YMRS. They were more likely to display an irritable mood than an elevated mood, which is consistent with earlier reports on patients with HIV-related mania (9–12). They were also more aggressive and disruptive, more over-

talkative, and more likely to have decreased need for sleep, and they had higher rates of paranoid delusions, visual hallucinations, and auditory hallucinations. Despite their severe psychopathology, they were more likely to have shorter hospitalizations. Previous researchers have reported that clinically HIV-positive individuals with AIDS mania had psychomotor slowing and were less talkative than patients with primary mania (9–11). Others have reported that the symptoms of first-episode secondary mania among HIV-positive individuals appeared to be similar to those of primary mania (12). However, none of these studies included a control group of HIV-negative individuals with primary mania.

The HIV-positive patients with secondary mania had greater cognitive impairment than the HIV-negative patients with primary mania, even after adjustment for education status. Only 15.9% appeared to have normal cognitive functioning, compared with 54.8% of HIV-negative individuals with primary mania. This difference between the two groups could be due to HIV-associated minor cognitive/motor disorder or HIV-associated dementia among the HIV-positive individuals. Although rates of HIV dementia have decreased in developed countries, in Uganda, a high rate (30%) has been reported for HIV-positive patients attending an HIV clinic at Mulago Hospital (21). In previous studies, HIV-positive patients with secondary mania have also had HIV dementia diagnosed (9, 10, 12), leading to suggestions that the development of secondary mania in HIV/AIDS patients is an initial stage of the HIV dementia process. Researchers have postulated that in the late stages of HIV illness, secondary mania is linked to HIV infection of the brain (9), a hypothesis supported by the finding that antiretroviral drugs that cross the blood-brain barrier may have a protective effect against secondary mania in patients with HIV infection (13).

The majority of our HIV-positive patients (55, or 90%) did not have HIV-related illnesses other than the mania, which is consistent with a previous report (10). Earlier case reports in the literature (22, 23) described additional HIV-related illnesses among patients with secondary mania, such as HIV wasting syndrome, *Pneumocystis carinii* infection Kaposi's sarcoma, and cryptococcal meningitis. These illnesses were not seen among the patients in our study, however. It may be that differences in opportunistic infections represent a difference in endemic disease states between developed and developing countries.

Several limitations of this study must be acknowledged. First, reports of personal and family histories of mental illness are limited by the potentially distorting influence of retrospective recall bias. Second, given the selected nature of the sample and the hospital setting in which the study was conducted, the results may not be generalizable beyond this study population. Third, our study sample was not assessed for brain pathology, which is recommended as part of the standard medical workup of new-onset psychiatric syndromes in patients with HIV infection. However, all patients studied had a neurological examination and were found to be fully conscious without focal neurological signs.

To our knowledge, this is the first study to describe the clinical presentation and correlates of first-episode secondary mania in a sample of HIV-positive patients in Africa. In summary, these patients were predominantly female, age 30–49 years, and of low socioeconomic and educational status. A significant number were divorced or had been widowed as a result of losing spouses to AIDS. Clinically, the majority presented in late stages of HIV infection, in WHO clinical stages 3 and 4; they were irritable and had aggressive and disruptive behaviors, decreased need for sleep, overtalkativeness, and high rates of cognitive impairment, paranoid delusions, visual hallucinations, and auditory hallucinations as well as high rates of HIV-related signs and symptoms. These findings show that first-episode secondary mania in HIV-positive individuals and primary mania in HIV-negative individuals are clinically and immunologically distinct. The relation between secondary mania and depressed CD4 counts suggests that in the setting of an AIDS epidemic in poor countries where the costs of measures of immune status, such as CD4 cell counts, are prohibitive, secondary mania may be used as an indicator to initiate highly active antiretroviral therapy.

Knowledge about the presentation of secondary mania in HIV infection may improve its clinical recognition and hence guide the development of early, effective interventions to control symptoms that not only interfere with a patient's ability to adhere to treatment but also predispose patients to HIV risk behaviors, which may lead to further spread of HIV infection. The number of cases of secondary mania in HIV infection we identified—61 patients in a 6-month period—suggests that this neuropsychiatric complication is not rare in Uganda. These circumstances call for the development of mental health services that are tailored to the needs of HIV-positive patients with mental illness as well as further research into the epidemiology, risk factors, and treatment outcomes of HIV-related secondary mania.

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CME Disclosure

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