

Delirium in HIV-infected patients admitted to acute medical wards post universal access to antiretrovirals in South Africa

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Background. Delirium is associated with increased mortality and length of hospital stay. Limited data are available from HIV-infected acute hospital admissions in developing countries. We conducted a prospective study of delirium among acute medical admissions in South Africa (SA), a developing country with universal antiretroviral therapy (ART) access and high burdens of tuberculosis (TB) and non-communicable disease.

Objectives. To identify the prevalence of, risk factors for and outcomes of delirium in HIV-infected individuals in acute general medical admissions.

Methods. Three cohorts of adult acute medical admissions to Groote Schuur and Victoria Wynberg hospitals, Cape Town, SA, were evaluated for prevalent delirium within 24 hours of admission. Reference delirium testing was performed by either consultant physicians or neuropsychologists, using the Confusion Assessment Method.

Results. The study included 1 182 acute medical admissions, with 318 (26.9%) HIV-infected. The median (interquartile range) age and CD4 count were 35 (30 - 43) years and 132 (61 - 256) cells/ μ L, respectively, with 140/318 (44.0%) using ART on admission. The prevalence of delirium was 17.6% (95% confidence interval (CI) 13.7 - 22.1) among HIV-infected patients, and delirium was associated with increased inpatient mortality. In multivariable logistic regression analysis, factors associated with delirium were age \geq 55 years (adjusted odds ratio (aOR) 6.95 (95% CI 2.03 - 23.67); $p=0.002$), and urea \geq 15 mmol/L (aOR 4.83 (95% CI 1.7 - 13.44); $p=0.003$), while ART use reduced risk ($p=0.014$). A low CD4 count, an unsuppressed viral load and active TB were not predictors of delirium; nor were other previously reported risk factors such as non-opportunistic acute infections or polypharmacy.

Conclusions. Delirium is common and is associated with increased mortality in HIV-infected acute medical admissions in endemic settings, despite increased ART use. Older HIV-infected patients with renal dysfunction are at increased risk for inpatient delirium, while those using ART on admission have a reduced risk.

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The prevalence of delirium in acute medical inpatients is high, with estimates ranging from 10% to 31%.^[1] Short- and long-term complications of delirium include increased mortality and length of hospitalisation, post-discharge institutionalisation, and long-term functional and cognitive decline.^[2] This is a considerable healthcare burden: in developed countries the cost of delirium is equal to that of falls and diabetes mellitus.^[3] A number of risk factors for delirium have been identified, including predisposing factors such as dementia and advancing age and acute precipitating factors such as drugs, infections and metabolic abnormalities.^[2] Protective factors include a higher level of education, a marker of cognitive reserve.^[4] Unfortunately, the data on delirium outcomes and risk factors in general medical inpatients are derived almost exclusively from geriatric populations in developed countries, a very different population to acute medical admissions in developing country settings with a high HIV/tuberculosis (TB) burden.^[5] Furthermore, the few studies from developing country settings such as sub-Saharan Africa (SSA) have either been conducted in medical patients aged

>60 years or in specialised populations, such as psychiatric and intensive care settings.^[6-8] In developed countries such as the USA, studies were done among HIV-infected populations before universal access to combination antiretroviral therapy (ART).^[9-14]

HIV targets the central nervous system (CNS) with resultant neurocognitive impairment (NCI), a well-described predisposing risk factor for delirium. Acute and opportunistic infections (OIs), also known risk factors for delirium, occur more commonly with advancing immunosuppression. It is therefore unsurprising that studies have shown high prevalence rates of delirium (3.7 - 57%) in HIV-infected populations.^[6,11-13] Delirium in HIV is often concomitant with NCI, in 8 - 22% of cases.^[15] Combination ART both prevents and improves NCI and decreases the incidences of acute and OIs. Widespread access to ART may therefore mitigate delirium risk. It is unclear whether HIV infection remains an independent risk factor for delirium in acute medical admissions in endemic HIV settings with universal ART programmes.^[9] Furthermore, in developing country settings such as South Africa (SA), with high

burdens of communicable diseases (CDs) and non-communicable diseases (NCDs), clinicians do not know which delirium risk factors to identify among HIV-infected admissions. Available data almost exclusively predate universal ART access.^[9-13,16] Furthermore, data from SSA populations are highly variable, owing to a lack of standardised delirium testing methods or incomplete HIV testing.^[6]

Objectives

We therefore conducted a study among acute medical admissions with a high HIV burden, using standardised delirium diagnostic testing methods, in a country with universal access to ART. The objectives were to identify the prevalence of, risk factors for and outcomes of delirium in HIV-infected individuals admitted to SA hospitals.

Methods

Study design and participants

This prospective cohort study focused on HIV-infected acute general medical admissions. The study was a secondary analysis within a parent prospective randomised cohort study designed for the development and validation of a novel four-question delirium screening tool. Prevalent delirium at admission was assessed using the Confusion Assessment Method (CAM) as the primary reference test to identify patients with delirium. A computer-generated random selection of daily acute general medical admissions to two hospitals (Groote Schuur Hospital (GSH) and Victoria Wynberg Hospital (VWH)) in Cape Town, SA, were enrolled for the parent study during two phases: 22 August 2009 - 10 December 2009 (development) and 11 November 2013 - 7 March 2014 (validation). GSH is a tertiary

referral hospital with ~150 acute general medical admission beds, while VWH is a district-level hospital with ~80 acute general medical beds. All adult medical patients aged ≥ 18 years admitted on weekdays were eligible, and a random sample of 10 patients per day was selected (usual daily patient intake 15 - 25 patients) to allow study staff to perform delirium testing within 24 hours of admission. Exclusion criteria were: (i) informed consent declined; (ii) age < 18 years; (iii) Glasgow Coma Scale score ≤ 12 ; and (iv) aphasia (Fig. 1).

The primary studies were approved by the University of Cape Town-Groote Schuur Hospital Human Research Ethics Committee (ref. no. 311/2017). If a patient was diagnosed with delirium during reference testing, their initial consent was not considered valid and the HREC granted an initial waiver of the informed consent requirement. When the patient's delirium had resolved, the study was explained to the patient again and written informed consent was obtained. If this was not possible as part of the initial inpatient admission, the patient and/or next of kin were contacted and arrangements were made to complete consent either in person or telephonically. If the patient was uncontactable, the HREC granted a waiver to allow the inclusion of patient data. There was no patient involvement.

All data relevant to the study are included in the article or have been uploaded as supplementary information (Appendices 1 - 5, available at <http://samj.org.za/public/sup/15628.pdf>).

Delirium testing

Within 24 hours of admission, a study physician reviewed the patient's charts and obtained data pertaining to the primary diagnosis, clinical background, admission medication, level of education

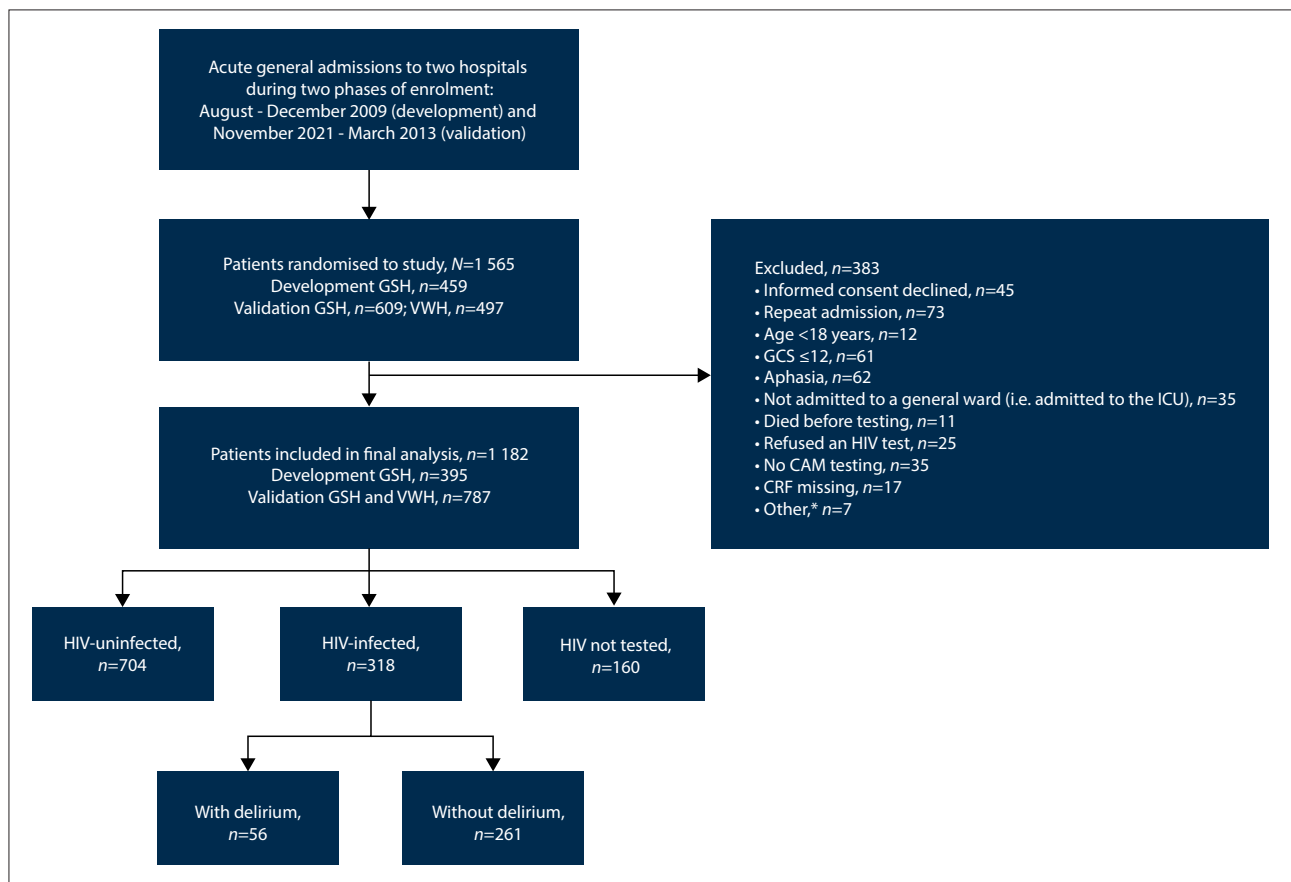


Fig. 1. Consort diagram. (GSH = Groote Schuur Hospital; VWH = Victoria Wynberg Hospital; GCS = Glasgow Coma Scale score; ICU = intensive care unit; CAM = Confusion Assessment Method; CRF = case report form; *Language barrier, deaf, elective admission.)

and demographic characteristics. A second independent study physician trained in delirium testing (in the development study) or a neuropsychologist (in the validation study) then assessed the patient for delirium using the CAM, performed during a 20 - 30-minute interview consisting of formal cognitive testing.^[17] For either testing tool the presence of language barriers was noted (see Fig. 1), or a ward-based translator was used when possible so that testing was performed in the patient's first language. Because delirium has, by its very nature, a fluctuating course of symptoms, patients were screened twice in 24 hours. However, there is still a possibility that some cases of delirium were missed owing to episodes of lucidity.

HIV status, diagnostic, medication and outcome data acquisition and classification

Investigations, including HIV screening and testing, were performed at the discretion of the attending physicians, and any patients who refused HIV testing during this admission were excluded from the study. Positive HIV status was defined as any record of a positive HIV test (either a rapid test or enzyme-linked immunosorbent assay) at any point prior to or during an index admission dating back to January 2005 (the earliest available information on the National Health Laboratory Service electronic system). The CD4 count and HIV viral load (VL) closest to or during the index admission, to a maximum of 12 months preceding admission, was included.

The patients' primary diagnoses and medications were collected by reviewing admission case records, pharmacy records and discharge summaries and assigning *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (ICD-10) diagnosis codes. We analysed the association of delirium with the top five most frequent CDs and NCDs, considering known HIV-associated conditions separately. Categories of medications commonly linked to delirium were selected based on published literature,^[18] and all medications were assigned to groups as per the *South African Medicines Formulary*. Antiretrovirals (ARVs), anti-TB medication, and medication for prophylaxis of OIs (fluconazole and trimethoprim/sulfamethoxazole) were assessed as possible protective factors for delirium in HIV-infected patients. Detailed information on ICD-10 and medication groupings is provided in Appendices 1 and 2 (<http://samj.org.za/public/sup/15628.pdf>). Outcome mortality data were obtained from patient folders, the hospital electronic patient management system and the Western Cape Provincial death registry, which links a unique patient identification number with national death certificate records and system-wide electronic records.

Statistical analysis

Data were analysed in Stata 14.2 (StataCorp, USA). Categorical variables were summarised as frequencies and percentages. Sociodemographic and clinical characteristics and outcomes were assessed for differences between HIV-infected, HIV-uninfected, and HIV unknown patients overall and in those with delirium. The analysis was then restricted to HIV-infected patients ($n=318$) to compare sociodemographics, clinical characteristics and outcomes between cases with and without delirium. Associations between categorical variables were analysed using the χ^2 test and Fisher's exact test, as appropriate. The Wilcoxon rank-sum test or the Kruskal-Wallis test were used to compare continuous variables between two and three groups, respectively.

Univariable and multivariable logistic regression analyses were performed to identify risk factors for delirium in HIV-infected patients. Variables analysed in univariable analysis were considered *a priori*, and receiver operating characteristic (ROC) curve analysis

was used for age and urea to determine clinically relevant cut-off values. Variables were retained in the multivariable model if they were significantly associated with outcome ($p<0.05$) and did not have sparse data (renal failure) or were not strongly collinear (urea and creatinine, total medication and ARVs). Education ≥ 7 years and CD4 count were retained in the multivariable model regardless of significance owing to their clinical relevance. Odds ratios (ORs) were reported with 95% confidence intervals (CIs). A p -value <0.05 was regarded as statistically significant.

Results

A total of 1 565 patients were randomised to the parent study (459 and 1 106 in the development and validation phases, respectively) (Fig. 1). Of these, 383 were excluded and a total of 1 182 patients were considered as part of this analysis. The prevalence of HIV infection was 26.9% ($n=318/1 182$), with 44% ($n=140/318$) using ART on admission. Table 1 and Appendix 5 (<http://samj.org.za/public/sup/15628.pdf>) describe the cohort stratified by HIV status and then restricted to only patients with delirium. Overall, the median (interquartile range (IQR)) age was 49.5 (34 - 63.2) years, and 53.1% were female (Table 1). HIV-infected patients were younger than the HIV-uninfected and unknown groups (median (IQR) 35 (0 - 43) years v. 52.7 (38 - 64.7) years and 66 (55.5 - 75.3) years, respectively; $p=0.0001$). The median (IQR) CD4 count was 132 (61 - 256) cells/ μ L. The prevalence of delirium was 17.6% in HIV-infected patients compared with 13.8% in HIV-uninfected patients and 11.9% in patients with unknown HIV status ($p=0.161$). Overall inpatient and 12-month mortality was 6.2% ($n=72/1 182$) and 23.8% ($n=281/1 182$), respectively, with no difference by HIV status (Table 1). There was no loss to follow-up in either the inpatient or the 12-month mortality groups. Among HIV-positive patients (Table 2), delirium was associated with higher inpatient mortality (14.6% v. 5.4%; $p=0.036$), but although HIV-infected patients had a higher 12-month mortality, the result was not significantly different (33.9% v. 22.9%; $p=0.083$).

Table 1 and Appendix 5 (<http://samj.org.za/public/sup/15628.pdf>) show primary admission diagnoses, key laboratory parameters and the five most common admission medication categories. NCDs accounted for more hospital admissions than CDs (69.7% v. 27.8%; $p<0.0001$), and two distinct patient groups were evident. HIV-infected patients had low rates of NCDs and a high burden of TB and other CDs, such as meningitis/encephalitis. They also used more medication (15.1% on three or more medications) owing to the prescription of ARVs and greater use of anti-TB medication and antibiotics. In contrast, the older HIV-unknown group were predominantly admitted with NCDs, and non-steroidal anti-inflammatory and cardiac drug prescribing was higher than in HIV-positive patients ($p<0.0001$). These differences were present when comparing the overall patient population (Table 1) and when restricted to patients with delirium (Appendix 5, <http://samj.org.za/public/sup/15628.pdf>). These findings show that HIV-infected patients have a unique profile relative to HIV-uninfected general medical admissions.

HIV-infected patients are compared in Table 2 according to the presence or absence of delirium. The two groups were similar in terms of age, gender and education status. With the exception of renal failure, there were no significant differences in CD or NCD primary diagnoses. Similarly, although patients with delirium had lower median CD4 cell counts (104 cells/ μ L (95% CI 32 - 214) v. 150 cells/ μ L (95% CI 62 - 266); $p=0.1284$) and lower rates of HIV viral suppression (27.3% v. 40%; $p=0.519$), these differences were not statistically

Table 1. Comparison of HIV-infected, HIV-uninfected and HIV unknown groups

	All (N=1 182)	HIV-infected (N=318)	HIV-uninfected (N=704)	HIV not tested (N=160)	p-value
Age (years), median (IQR)	49.5 (34 - 63.2)	35 (30 - 43)	52.7 (38 - 64.7)	66 (55.5 - 75.3)	0.0001
Female, n (%)	627 (53.1)	197 (61.9)	335 (47.6)	95 (59.4)	<0.0001
Education ≥7 years, n (%)	830 (75.9)	230 (72.3)	488 (74.9)	112 (74.2)	0.332
Delirium present, n (%)	172 (14.6)	56 (17.6)	97 (13.8)	19 (11.9)	0.161
Dementia/cognitive deficit, n (%)	52 (4.4)	8 (2.5)	24 (3.4)	20 (12.5)	<0.0001
Primary diagnosis,* n (%) (N=1 153)					
NCDs total	824 (69.7)	141 (44.3)	544 (77.3)	139 (86.9)	<0.0001
4 most common NCDs					
CVS combined	238 (20.1)	29 (9.1)	149 (21.2)	60 (37.5)	<0.0001
Respiratory	94 (8.0)	11 (3.5)	72 (10.2)	11 (6.9)	0.001
Cerebrovascular	70 (5.9)	4 (1.3)	49 (7.0)	17 (10.6)	<0.0001
Renal failure	42 (3.6)	9 (2.8)	30 (4.3)	3 (1.9)	0.293
CDs total	329 (27.8)	142 (44.7)	165 (23.44)	22 (13.8)	<0.0001
4 most common CDs					
TB, total	145 (12.3)	92 (28.9)	51 (7.2)	2 (1.3)	<0.0001
Pulmonary TB	75 (6.4)	35 (11)	39 (5.5)	1 (0.6)	<0.0001
TB meningitis	20 (1.7)	15 (4.7)	5 (0.7)	0	<0.0001
Disseminated TB	33 (2.8)	28 (8.8)	5 (0.7)	0	<0.0001
Pneumonia	88 (7.5)	27 (8.5)	52 (7.4)	9 (5.6)	0.528
Meningitis/encephalitis	21 (1.8)	11 (3.5)	9 (1.3)	0	0.040
UTI	20 (1.7)	0	16 (2.3)	4 (2.5)	0.005
Laboratory results, median (IQR)					
WCC (/10 ⁹ /L) (n=1 124)	9.2 (7.1 - 11.6)	8 (5.7 - 9.6)	9.5 (7.6 - 12.4)	9.6 (8.5 - 12.4)	0.0001
Hb (g/dL) (n=1 122)	11.3 (9.4 - 13.8)	9.8 (8.5 - 11.7)	12.1 (9.6 - 14.1)	12.7 (9.8 - 14.4)	0.0001
Sodium (mmol/L) (n=1 102)	138 (135 - 141)	135 (132 - 139)	139 (135 - 141)	140 (138 - 143)	0.0001
Urea (mmol/L) (n=1 101)	7.1 (4.7 - 9.7)	5.9 (4 - 8.9)	7.2 (4.9 - 9.8)	8.5 (6.6 - 9.8)	0.0001
Medication, n (%)					
Absolute number of medications ≥3	90 (7.6)	48 (15.1)	28 (4)	14 (8.8)	<0.0001
5 most common admission medications [†]					
NSAIDs	230 (19.5)	9 (2.8)	138 (19.6)	83 (51.9)	<0.0001
Cardiac medications	169 (14.3)	6 (1.9)	109 (15.5)	54 (33.8)	<0.0001
Steroids	131 (11.1)	11 (3.5)	101 (14.4)	19 (11.9)	<0.0001
TB medications	99 (8.4)	62 (19.5)	36 (5.1)	1 (0.6)	<0.0001
Antibiotics	62 (5.3)	49 (15.4)	13 (1.9)	0	<0.0001
Mortality, n (%)					
Inpatient	72 (6.2)	22 (7.0)	40 (5.8)	10 (6.3)	0.7540
12 months	281 (23.8)	79 (24.8)	167 (23.7)	35 (21.9)	0.7710

IQR = interquartile range; NCDs = non-communicable diseases; CVS = cardiovascular system; CDs = communicable diseases; TB = tuberculosis; UTI = urinary tract infection;

WCC = white cell count; Hb = haemoglobin; NSAIDs = non-steroidal anti-inflammatory drugs.

*See Appendix 1 (<http://samj.org.za/public/sup/15628.pdf>) for detailed diagnoses.

[†]See Appendix 2 (<http://samj.org.za/public/sup/15628.pdf>) for details of medications.

significant. However, the delirium group had significantly lower haemoglobin ($p=0.0194$) and higher urea ($p=0.0047$) and creatinine levels ($p=0.0197$). A higher number of patients without delirium were using three or more admission medications ($n=45$; 17.2% v. $n=3$; 5.4%; $p=0.023$), with a greater number of patients on ARVs, antibiotics, and OI prophylaxis (trimethoprim/sulfamethoxazole and fluconazole). However, use of TB medication in the two groups was similar (19.6% v. 19.5%; $p=0.976$).

Table 3 shows the univariable and multivariable logistic regression analysis used to analyse associations with prevalent delirium in HIV-infected acute medical admissions. For every 5-year increase in age there was a 12% increased risk of delirium (95% CI 0.99 - 1.30; $p=0.065$), with an adjusted odds ratio (aOR) of 6.95 (2.03 - 23.67) using an ROC-selected age ≥55 years ($p=0.002$). On univariable analysis, both a primary diagnosis of renal failure (OR 6.3 (95% CI 1.6 - 24.4);

$p=0.007$) and ROC-selected urea ≥15 mmol/L increased the risk of delirium, with only urea >15 mmol/L retained in the multivariable analysis (aOR 4.83 (95% CI 1.7 - 13.44); $p=0.0003$). Patients using three or more medications on admission had a decreased risk of delirium (OR 0.3 (95% CI 0.1 - 0.9); $p=0.035$), with the greatest protective effect from the use of ART on admission (aOR 0.34 (95% CI 0.14 - 0.8); $p=0.014$). Other NCDs and CDs, including TB, or markers of advanced immunosuppression and poor HIV control (CD4 cell count and VL suppression), were not significant risk factors for delirium.

Discussion

Our study is the first to study delirium, using a validated testing method, among HIV-infected inpatients admitted in the context of an acute general medical intake in a developing country with dual CD

Table 2. Comparison of HIV-infected groups with and without delirium

	HIV-infected with delirium (N=56)	HIV-infected without delirium (N=261)	p-value
Age (years), median (IQR)	34 (30 - 43.1)	34.6 (29.4 - 41.7)	0.373
Female, n (%)	33 (58.9)	164 (62.6)	0.608
Education ≥7 years, n (%)	28 (73.7)	202 (79.8)	0.385
Primary diagnosis (N=337),* n (%)			
Non-communicable total	23 (41.2)	118 (45.0)	0.588
4 most common NCDs			
CVS combined	2 (3.6)	27 (10.3)**	0.131
Respiratory	0	11 (4.2)	0.223
Renal failure	5 (8.9)	4 (1.5)	0.010
Liver failure	0	5 (1.9)	0.591
Communicable total	28 (50.0)	114 (43.5)	0.375
2 most common CDs			
TB total	18 (32.1)	74 (28.2)	0.559
Pulmonary TB	5 (8.9)	30 (11.5)	0.814
TB meningitis	4 (7.1)	11 (4.2)	0.312
Disseminated TB	7 (12.5)	21 (8)	0.299
Pneumonia	7 (12.5)	20 (7.6)	0.287
HIV-specific diagnoses,‡ n (%)	10 (17.9)	44 (16.8)	0.847
2 most common§			
CCM	3 (5.4)	8 (3.1)	0.417
HAND	4 (7.14)	6 (2.29)	0.079
Laboratory results, median (IQR)			
CD4 (cells/µL) (n=302)	104 (32 - 214)	150 (62 - 266)	0.1284
Viral suppression (%)† (n=86)	3 (27.3)	30 (40)	0.519
WCC (/10 ⁹ /L) (n=309)	8.3 (5.9 - 9.7)	8 (5.7 - 9.5)	0.6299
Hb (g/dL) (n=308)	9.5 (8.1 - 10.3)	9.8 (8.7 - 12.1)	0.0194
Sodium (mmol/L) (n=297)	134.5 (131 - 140)	135 (132 - 139)	0.3279
Urea (mmol/L) (n=297)	7.2 (4.5 - 16.7)	5.7 (3.9 - 8.5)	0.0047
Creatinine (µmol/L) (n=306)	83 (65 - 208)	76 (58 - 94)	0.0197
CRP (mg/L) (n=185)	76.2 (28.9 - 135.2)	45.7 (20 - 107.1)	0.3522
Admission medication,‡ n (%)			
Absolute number of medications ≥3	3 (5.4)	45 (17.2)	0.023
ARVs	14 (25.0)	126 (48.1)	0.002
Trimethoprim/sulfamethoxazole	3 (5.4)	38 (14.5)	0.078
TB medications	11 (19.6)	51 (19.5)	0.976
Antibiotics	4 (7.1)	45 (17.2)	0.067
Mortality, n (%)			
Inpatient	8 (14.6)	14 (5.4)	0.036
12 months	19 (33.9)	60 (22.9)	0.083

IQR = interquartile range; NCDs = non-communicable diseases; CVS = cardiovascular system; CDs = communicable diseases; TB = tuberculosis; CCM = cryptococcal meningitis; HAND = HIV-associated neurocognitive disease; WCC = white cell count; Hb = haemoglobin; CRP = C-reactive protein; ARVs = antiretrovirals.

*See Appendix 1 (<http://samj.org.za/public/sup/15628.pdf>) for detailed diagnoses.

†19 patients had dual primary diagnoses, i.e. CCM and pulmonary TB.

‡See Appendix 3 (<http://samj.org.za/public/sup/15628.pdf>) for details of HIV-specific diagnoses.

§All other diagnoses <3%.

¶Lower than detectable limit or <20 RNA copies/million.

**See Appendix 2 (<http://samj.org.za/public/sup/15628.pdf>) for details of medication.

***The diagnoses in this group were venous thromboembolic disease (29.6%), cardiac failure (29.6%), cardiomyopathy (11.1%) and pericarditis (11.3%).

and NCD burdens,^[5] and in the setting of improved access to ART. The key findings of our study are: (i) delirium occurred in 14.6% of all acute medical hospital admissions and 17.6% of HIV-infected patients (with 44% ART coverage); (ii) delirium was an independent risk factor for inpatient mortality among HIV-infected admissions; (iii) ART use at admission was protective against prevalent delirium; and (iv) age ≥55 years and urea >15 mmol/L were associated with an increased risk of delirium among HIV-infected admissions, rather than markers of advanced immunosuppression (low CD4 cell count), poor viral control (VL) or active TB. These findings should inform

clinical practice for generalists and HIV clinicians in developing country settings by allowing them to rapidly identify HIV-infected patients at risk for prevalent delirium.

Delirium prevalence rates vary widely between studies and are dependent on the delirium screening tool used, the study population and patient demographics, the burden of disease, and whether the study took place in a developing or developed world setting. No data are available on HIV-infected medical inpatients in the ART era. Our cohort delirium prevalence of 17.6% in HIV-infected patients is consistent with both the 4 - 30% published in a recent

Table 3. Univariable and multivariable analysis of risk factors for delirium in HIV-infected patients

Variable	Univariable, OR (95% CI)*	p-value	Multivariable, aOR (95% CI)	p-value
Age (per 5-year increase)	1.12 (0.99 - 1.3)	0.065		
Age ≥55 years	4.1 (1.6 - 11.1)	<0.0001	6.95 (2.03 - 23.67)	0.002
Education ≥7 years	0.71 (0.3 - 1.6)	0.386	0.76 (0.3 - 1.95)	0.583
Laboratory values				
CD4	0.99 (0.99 - 1)	0.241	0.84 (0.79 - 1.05)	0.22
Hb	0.9 (0.8 - 0.98)	0.025	0.91 (0.79 - 1.05)	0.22
Urea	1 (1 - 1.1)	0.008		
Urea ≥15 mmol/L	5.0 (2.3 - 10.7)	<0.0001	4.83 (1.7 - 13.44)	0.003
Medication				
ARVs	0.4 (0.2 - 0.7)	0.002	0.34 (0.14 - 0.8)	0.014

OR = odds ratio; CI = confidence interval; aOR = adjusted OR; Hb = haemoglobin; ARVs = antiretrovirals.
*See Appendix 4 (<http://samj.org.za/public/sup/15628.pdf>) for detailed univariable analysis.

review on delirium in SSA^[6] and the 12 - 57% in US studies^[12-15,19] in HIV-infected medical inpatients in the pre-ART era. The delirium rate was high despite ART coverage of 44% in our cohort. Studies show that in general medical wards delirium goes undiagnosed in 32 - 67% of patients and that this group of patients has an increased mortality rate.^[20] Lalonde^[11] found that only one of 46 HIV-infected patients was correctly diagnosed with delirium in a specialist HIV centre. These figures together should continue to highlight that even as ART coverage continues to improve, delirium surveillance in developing countries is an important health priority. In the UK, the National Institute for Health and Care Excellence (NICE) recommends risk factor and indicator assessment for all patients admitted to hospital,^[21] and incident delirium is used as a marker of good clinical governance.^[22]

We found that delirium was associated with increased inpatient mortality in HIV-infected patients as well as an (albeit non-significant) increase in 12-month mortality. This finding is in keeping with previous studies in older patients showing that delirium is related to significantly increased short- and long-term mortality.^[23,24] The mortality rates of our HIV-infected patients with delirium (33.9% at 12 months and 14.6% as inpatients) were far lower than the inpatient mortality rates reported by Uldall and colleagues^[9,19] in two studies on HIV-infected patients (63% and 97%, respectively), probably because our study was done in the era of universal access to ART. However, a significantly lower percentage of our HIV-infected patients with delirium were on ARVs at the time of admission compared with their non-delirious counterparts (25.0% and 48.1%, respectively). The protective effect of ART on delirium risk is not surprising, given its known benefit in terms of the NCI associated with HIV.^[25] These findings highlight the need to improve universal access to ART.

We found that older HIV-infected patients with acute renal dysfunction were at high risk for inpatient delirium, while those using ART on admission seemed to be protected. Similarly, on univariable analysis we found three known delirium risk factors to be important in our HIV-infected patients: older age, anaemia and uraemia. These findings are in keeping with data from Tanzanian and Indian general medical inpatient cohorts.^[7,26] Anaemia and uraemia are well-described risk factors for delirium, and anaemia is also a predictor of mortality in HIV-infected patients.^[2,27] Uraemia probably causes delirium as a result of uraemic encephalopathy, a poorly understood process that is thought to involve oxidative stress, hormonal and neurotransmitter imbalances, and the accumulation of toxic metabolites.^[28] However, in our cohort many typical risk factors (acute non-OIs, TB and hyponatraemia) were not predictors

of delirium. We also found that markers of advanced HIV (low CD4 count and unsuppressed VL) were not significant risk factors for delirium, in keeping with the one previous study that assessed CD4 count.^[9]

Interestingly, in our study we found that the more admission medications prescribed, the lower the risk of delirium. This high number of medications is probably attributable to the pill burden of combined ART and the requirement for OI antibiotic prophylaxis in HIV-infected patients. This finding is in clear contrast to the frequently reported link between polypharmacy and delirium in elderly populations;^[2] however, this increased risk was also reported in HIV-infected cohorts in which the use of three or more CNS active medications and medication side-effects were found to be key risk factors for delirium.^[9,11] Medications that significantly contributed to delirium in another study were benzodiazepines and narcotics,^[19] this was also not found in our study. Notably, all the above studies were in the pre-combination ART era^[29] and ART use was not reported.

Study limitations

The present study is to our knowledge the largest to date to conduct formalised delirium assessments in HIV-infected acute medical admissions. Nevertheless, despite the large overall study size, there were only 56 cases of delirium in the HIV-infected group. We therefore had limited power to detect small differences between groups, and the regression analysis findings should be interpreted with caution. Our findings will need validation in other developing HIV-endemic country settings. Another limitation was the lack of mandatory HIV testing on admission, leading to concern about possible inclusion bias. Fortunately, only 13.5% of patients were not tested for HIV in a large cohort, and there were few missing CD4 cell count data (but insufficient VL measurements). The HIV not-tested cohort was a group of older patients with more NCDs, fewer infections and less TB, and thought likely to be at low risk of HIV infection by the attending clinicians. Although assessing prevalent delirium on admission may be difficult owing to incomplete available information as well as the fluctuating nature of the condition, a further period of observation would only be expected to increase this prevalence.

Conclusions

Delirium is highly prevalent and poorly recognised, and has high morbidity and mortality that carry a significant cost to healthcare systems.^[3] We have shown that even with improved ART coverage in a developing country setting with a dual burden of HIV and TB,

delirium is common and is associated with inpatient mortality in HIV-infected patients. Clinicians need to be aware that ageing HIV-infected patients who are not on ART and who have renal failure are at risk for delirium. In addition, a low CD4 count and elevated VL do not increase the likelihood of delirium. Further delirium research using a standardised testing method is required to validate these findings in other developing countries.

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Author contributions. JGP designed and led the development study. GC assisted with enrolling patients and collected data. JGP and PR designed and led the validation study. FA, KJ, LG and CD enrolled patients and collected data for the validation study. CD, FA and CA entered and collated the original data. CD and JGP designed and wrote the study protocol. CD and KM analysed and interpreted data. CD wrote the first draft of the report. MC assisted with parent study design and editing. All authors reviewed and approved the final version.

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