Delirium amongst HIV-infected general medical admissions in Cape Town, South Africa

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Declaration of originality

I, Cascia Day, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background

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

Methods

Three cohorts of adult acute medical admissions to Groote Schuur and Victoria Hospitals, Cape Town, South Africa 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 (CAM).

Findings

The study included 1182 acute medical admissions; with 318 (26·9%) HIV-infected Median(IQR) age and CD4 count was 35(30-43) years and 132(61-256) cells/mm3 respectively, with 140/318(44%) using ART on admission. Delirium prevalence was 17·6%(95% CI 13·7-22·1%) amongst HIV-infected patients and was an independent risk factor for inpatient mortality. In multivariable logistic regression, factors associated with delirium were age ≥55 years(AOR 6·95[2·03-23·67], p=0·002) and urea ≥15(AOR 4·83[1·7-13·44], p=0·003), while ART use reduced risk (p=0·014). Low CD4 count, unsuppressed viral load, and active TB were not predictors of delirium; nor were other traditional risk factors such as non-opportunistic, acute infections or polypharmacy.

Interpretation

Delirium is common and predicts poor outcome in HIV-infected acute medical admissions in endemic settings despite increased ART use. Older HIV-infected patients with renal dysfunction are at high risk for inpatient delirium while those using ART on admission are protected.

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Contributions

A/Prof Peter designed and implemented the development study. A/Prof Peter and A/Prof Raubenheimer designed and led the validation study. Faried Abdullah and Cascia Day enrolled patients and collected data for the validation study. Cascia Day, Faried Abdullah, Nadia Vorajee, and Caryn April entered and collated original data. Cascia Day and A/Prof Peter designed and wrote the MMed study protocol. Cascia Day and Kathryn Manning analysed and interpreted data. Cascia Day wrote the first draft of the report and all authors reviewed and approved the final version.

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Abbreviations

AIDS	Acquired Immuno-Deficiency Syndrome
ART	Anti-Retroviral Therapy
ARVs	Anti-Retrovirals
CAM	Confusion Assessment Method
CCM	Cryptococcal meningitis
CD	communicable disease
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CVS	cardiovascular system
GABA	Gamma-Aminobutyric acid
GSH	Groote Schuur Hospital
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic – pituitary-axis
ICU	Intensive care unit
IGF-1	Intrinsic growth factor -1
IL-1RA	Interleukin-1 receptor antagonist
IL-8	Interleukin-8
INF γ	Interferon gamma
IQR	Inter-quartile range
MODs	Major Organ Dysfunction
NCDs	non-communicable diseases
NCI	Neuro-cognitive Impairment
NSAIDs	Non-steroidal anti-inflammatory drugs
OIs	opportunistic infections
OMD	organic mental disorder
OR	Odds ratio
PJP	*Pneumocystis jerovici* pneumonia
RR	Relative Risk
SSA	Sub-Saharan Africa
TB	Tuberculosis
USA	United States of America
UTI	urinary tract infection
VL	HIV viral load
VWH	Victoria Wynberg Hospital
WCC	white cell count
WHO	World Health Organisation

Chapter One: Background and Literature Review

Background

Introduction

Delirium is a heterogeneous, fluctuating syndrome of acute brain failure.(1) Patients with delirium have deranged attention, orientation, cognition, and sleep-wake cycles, as well as psychomotor and behavioural problems.(2-5) Delirium is often viewed as a complication of in-patient care and a marker of the quality of care.(6) Current literature generally focuses on studies in developed countries within geriatric and intensive care populations. The prevalence of delirium is variable, with rates of 10-31% in medical inpatients, 40% in nursing homes, and up to 80% in ICU settings.(7, 8) This common disorder has significant long term and short term complications, and a high mortality rate.(6)

Delirium pathophysiology

The pathophysiology of delirium has not been clearly defined. The clinical presentation of delirium may represent Central Nervous System (CNS) reactions to central or peripheral stressors, with interaction between central and peripheral pathways. There are multiple hypotheses regarding the pathophysiology of delirium, but these theories can be broadly separated into: Neurotransmitter hypothesis and Immune-inflammation dysregulation.

Neurotransmitter hypothesis

In the neurotransmitter hypothesis precipitating events lead to oxidative stress in the CNS and changes in concentration of various neurotransmitters. This theory arises from the observation of delirium as a side effect in a variety of drugs that directly affect

neurotransmitters (e.g. anti-cholinergic drugs and dopamine agonists).(9, 10) Underactivity of the cholinergic system and excess release of dopamine, norepinephrine, and glutamate with both increased/decreased serotonergic and gamma-aminobutyric acid activity may be risk factors for delirium.(9-14)

The Immune-inflammation dysregulation theory

The Immune-inflammation dysregulation theory draws a link between sickness behaviour and delirium. Sickness behaviour includes: malaise, increased somnolence, decreased cognitive ability, low mood, social withdrawal, decreased motor activity, anorexia, and fever.(15, 16) These behavioural and neuro-endocrine changes are exaggerated in delirium due to aberrant homeostasis. Immune-inflammation dysregulation is hypothesised to include: an increased pro-inflammatory milieu, Hypothalamic pituitary-axis (HPA) derangement, and microglial cell dysfunction.

Sickness behaviour changes are triggered by a predominance of pro-inflammatory cytokines. Elevated levels of IL-8, INF γ, CRP, low baseline IGF-1, and IL-1RA levels have been found to be predictive of delirium.(16, 17) Anti-inflammatory cytokines act by downregulating ischaemic and excitotoxic neural damage, and inhibiting the induction of the inflammatory reaction by amyloid β peptide.(16-19)

Aged patients, or those with neurodegenerative disease, have a more pronounced response to systemic inflammation; this observation has been supported by animal models.(15, 20) Part of this exaggerated response is thought to be HPA over activity, and impaired negative feedback, combined with sustained high levels of cortisol in response to peripheral stressors.(9) Elevated endogenous and exogenous cortisol can cause cognitive impairment

and neuropsychiatric disease. Cortisol is also elevated in patients with neurodegenerative disease.

Microglial cells are the resident CNS macrophages, these cells are primed by chronic neurodegenerative disease to increase in number and express more markers of phagocytosis.(9) It is hypothesised that microglia are primed in the aged, or those with neurodegenerative disease, to amplify the CNS inflammatory response to a peripheral insult.(15, 21, 22)

The pathophysiology of delirium is complex and poorly understood; further study in this area could elucidate possible markers of delirium severity and/or markers to help identify patients who are at risk of delirium.

Delirium risk factors

While a single noxious event can precipitate delirium, the aetiology is most often multifactorial.(2) The risk factors for delirium can be divided into two categories: predisposing factors and precipitating factors and are described in *Table 1*.

Table 1: Risk factors for Delirium in Medical patients[†]

Risk factors for delirium in medical patients	
Predisposing	**Precipitating**
Older age Cognitive dysfunction - Dementia - Depression - Intellectual impairment Sensory deficits - Hearing - Vision Functional impairment Severity of illness Number of co-morbid illnesses Frailty Male gender Previous delirium Psychotropic drug use	Infection Metabolic abnormalities - Hypoxia - Hypercarbia - Electrolyte abnormalities e.g. Sodium - Organ Dysfunction e.g. elevated urea and ammonia in kidney and liver failure, respectively - Endocrinopathies, especially elevated cortisol - Malnutrition Cerebral insults - Stroke: infarct / haemorrhage - Infection - Trauma Iatrogenic - Adding > 3 medications - Use of anticholinergics, sedation, opiates, corticosteroids and NSAIDs - Restraints - Indwelling catheter - Poor pain management Constipation and urinary retention Environmental changes

[†](1, 5, 7, 13, 23-27)

Patients with cognitive dysfunction, especially dementia, are at a higher risk of delirium. These patients develop delirium in response to minor stimuli, and tend to have a protracted course of delirium with more severe and longstanding cognitive decline.(13) Conversely, patients with a higher level of education (a marker of cognitive reserve) have been found to

be at lower risk of delirium: Jones *et al*. found that each year of completed education was associated with lower odds of delirium OR 0.91 (95% CI: 0.87-0.95, $p<0.01$).(28) However, at least one other study found that education offers no protection from delirium.(29)

Drugs are the most common and reversible cause of delirium, accounting for 12%–39% of all cases.(30) A recent systematic review found that when psychoactive medications (anticholinergics, benzodiazepines, opioid analgesics, steroids, antidepressants, antipsychotics, and antihistamines) were grouped as a variable there was a significantly increased risk of delirium in five studies. However, the review was under powered, limited by the heterogeneity of the studies, and inconsistent statistical analyses.(31) Drugs with anticholinergic activity are well described as causes of delirium,(9, 10) while Benzodiazepine use has been found to be an independent risk factor for cognitive impairment with an adjusted OR of 3.5 (95% CI: 1.4-8.8).(32) Table 2 presents a summary of groups of medications known to cause delirium, and their presumed mechanism of action.

Table 2: Examples of medications that cause delirium†

Group of medication	Examples	Mechanism
Antiparkinsonian agents	Carbilevadopa	Excess dopaminergic activity
Analgesics	NSAIDs Morphine	Anticholinergic activity GABA antagonism
Antidepressants	Serotonin release inhibitors Tricyclic antidepressants	Serotonergic dysfunction Anticholinergic activity
Antihistamines	Diphenhydramine	Anticholinergic activity
Antispasmodic agents	Hyoscyamine	Anticholinergic activity
Antipsychotics	Haloperidol Olanzapine	Anticholinergic activity Anticholinergic activity
Bronchodilator	Theophylline	Anticholinergic activity
Cardiac medication	Beta-blockers Amiodarone Digoxin	Anticholinergic activity Anticholinergic activity Anticholinergic activity
Corticosteroids	Dexamethasone	Anticholinergic activity
Dopaminergic agents	Bromocriptine	Excess dopaminergic activity
Prokinetics	Metoclopramide	Dopamine receptor antagonist Excess glucocorticoid activity
Sedatives	Lorazepam Midazolam	GABA antagonism GABA antagonism

†(30, 33, 34)

Prevalence of delirium

Current delirium literature generally focuses on studies in developed countries within geriatric and intensive care populations. The prevalence of delirium is variable, with rates of 40% in nursing homes and up to 80% in ICU settings.(7, 8) A recent systematic review by Siddiqi *et al.*(8) looked at 21 studies from 1982 to 2005 in general medical wards. This review found that delirium was prevalent in 10-31% of medical inpatients. All but one of the studies was based in developed/high income countries with all patients older than 65 years of age. The screening, diagnostic methodology, and methods of describing delirium were highly variable between the studies.

Impact of Delirium

This common disorder has many short and long term complications. In the short term, delirium results in increased length of hospital stay, greater use of psychical restraints, continuous sedation, and has higher rates of complications. These patients have increased mortality,(2) with studies showing mortality rates at discharge of 14.5 to 37%.(8, 23) Long term complications include prolonged delirium (up to 12 months), post discharge institutionalisation, as well as functional and cognitive decline. Patients diagnosed with delirium have higher rates of future dementia and a 1.5-fold increased risk of death in the year following hospitalization.(1, 2, 7, 8, 26) The mortality rate is higher in the following cases: undetected delirium, hypoactive delirium, young patients, and patients who are restrained.(1, 23) Literature also shows that between 32-67% of delirium cases remain unrecognised in general medical wards.(35) Not only does delirium have serious implications for patients, health care systems also carry the burden of this disease. In the United States patients with delirium have an average hospital cost per day survived of 2.5 times that of non-

delirious patients. The burden on the health care system in developed countries rivals the cost of falls and diabetes mellitus.(36)

Delirium is a common, serious medical condition that is often misdiagnosed in a clinical setting, and is associated with poor short and long term outcomes, higher risk of mortality, and increased health care costs.(8)

Delirium in developing countries

There has been little research done in delirium in medical inpatients in Sub-Saharan Africa (SSA), with the majority of studies being conducted in psychiatry and intensive care settings.(37-40). Paddick *et al.*(37) recently published a systematic review of 46 papers from 16 SSA countries with the majority of the papers coming from Nigeria (n=15), South Africa (n=6), and Senegal (n=5). The review contains several limitations, namely that delirium was the main focus of only one cross-sectional study; there was no standard criteria used for diagnosis of delirium, and most of the patients investigated were not tested for HIV. Several studies on the delirium rates on Sub-Saharan African cohorts have shown that there is a high variability in the rates of delirium between population groups. Notably, the rates of delirium in SSA are 3.7-29.9% in psychiatric patients,(37, 39, 40) 15 % in palliative care patients,(41) and 51% in an intensive care setting.(38) A recent study looking at delirium in older acute medical admissions (>60years of age) in Tanzania found a delirium prevalence of 19.2% (95%CI: 15.7 – 22.7).(42) Despite these studies, and an extensive literature review, there is no data on the prevalence, risk factors for, and outcomes of delirium in the HIV positive general medical in-patients in SSA.

The most common risk factors for delirium are dementia, polypharmacy/medication side effects, infection and metabolic dysfunction.(43) A systematic review from SSA found the

most common risk factors for delirium were HIV (3.7–30.1%), patients admitted for palliative care (15%), Typhoid (14%), liver disease (12.9%), heart disease (12.5%), and Malaria (10%).(37) While a recent study on older medical in patients in Tanzania found that significant risk factors for delirium in their population were similar to risk factors in high income countries. The most significant risk factors were: increasing age, male gender, pre-existing dementia, physical dependency, degree of illness severity, and current alcohol use.(42)

The outcomes of delirium are well described in high-income countries, but the outcomes of delirium in low-income countries are not readily available. In India, a research group investigating delirium in general medical wards, found that delirious patients had an inpatient mortality rate of 12.4% (41/331) with a mortality rate at 6 months of 28%, in two studies respectively.(44) Another Ugandan multicentre study of delirium in ICU patients found an inpatient mortality rate of 55.45%; however, the length of ICU stay was not significantly different to patients without delirium.(38) There are no studies about the outcomes of general medical patients with delirium in SAA.

HIV in South Africa

South Africa has one of the highest prevalence rates of HIV infection, with almost 20% of the global HIV positive population living in the country.(45) The number of HIV infected individuals has risen from 5.48 million in 2011 to 6.19 million in 2015, and the antenatal HIV seroprevalence in Khayelitsha in 2013 was 34.4%.(46, 47) A recent study in a Cape Town hospital showed that HIV still accounts for more than two thirds of total general medical admissions. The most common presenting diagnoses being AIDS defining illnesses (including: Tuberculosis (TB), bacterial infections, and Major Organ Dysfunction

(MODs)).(47) South Africa launched the National ART roll out programme in 2004, and by 2013 there were an estimated 2.3 million people on ART.(45) Between 2003 and 2011, after the roll out of ART, life expectancy in rural Kwa-Zulu Natal increased by 20% (from 49.2 to 60.5 years).(48) Due to the increased life expectancy and the fact that all HIV positive people now have access to ART regardless of CD4 count (based on the new national and WHO treatment guidelines),(45) there will soon be an aging HIV positive population that will be at higher risk for delirium.

Previously, South Africa's primary focus was on HIV incidence and prevalence in women of childbearing age, as this was assumed to be a high risk group.(49) However, a recent model showed that HIV prevalence in adults >50 years of age in SSA will triple by 2040 (from 3.1-9.1 million).(50) South Africa has the highest proportion of older people in its population than any other SSA country.(49) A 2012 survey by the South African Human Sciences Research Council found the prevalence of HIV in amongst adults aged 50-54 is 13%, while the average prevalence for all adults >50 years is 7.6%.(51) These prevalence rates are not significantly different to the 15-25 year age group (p=0.511), although the older age group has a higher percentage of males and residents of informal rural/urban areas (51) A survey conducted in rural KwaZulu-Natal found that being >65 years of age was an independent risk factor for a positive HIV status (adjusted OR 0.2, p<0.001) and the incidence rate of HIV in adults >50 years was 0.5 (95% CI 0.3 - 1.0) per 100 person-years overall.(52). There is a higher mortality rate in the older HIV population as they are more prone to TB, non-communicable diseases, and have a slower response to ARVs.(53, 54) Despite the high prevalence and incidence of HIV in this age group, there is a bias towards not screening for HIV in the elderly due to the perceived "low risk" of this group. The delayed diagnosis of

HIV in the elderly leads to lower CD4 counts at presentation and rapid progression of disease.(55)

In addition to the massive burden of HIV infection there has been an escalation of non-communicable diseases in South Africa. In 2012, The World Health Organisation estimated that non-communicable diseases (cardiovascular disease, cancers, chronic respiratory diseases, and diabetes) accounted for 48% of deaths in South Africa, with a 27% probability of dying from one the 4 main non-communicable diseases in the population aged 30 – 70 years.(56) Up to 30% of South African patients >50 years have two or more chronic conditions.(57) Although older patients are more likely to be adherent to medication, adherence is decreased in patients taking multiple medications.

In the years to come, South Africa will have an aging HIV positive population with a high burden of non-communicable diseases. This group will also be at risk for traditionally geriatric problems such as frailty, falls, dementia, and delirium.(58) Previous studies in SSA have shown that HIV and infections are risk factors for delirium, therefore it would be inferred that this aging HIV positive patients would be at higher risk of delirium.(37)

Literature Review

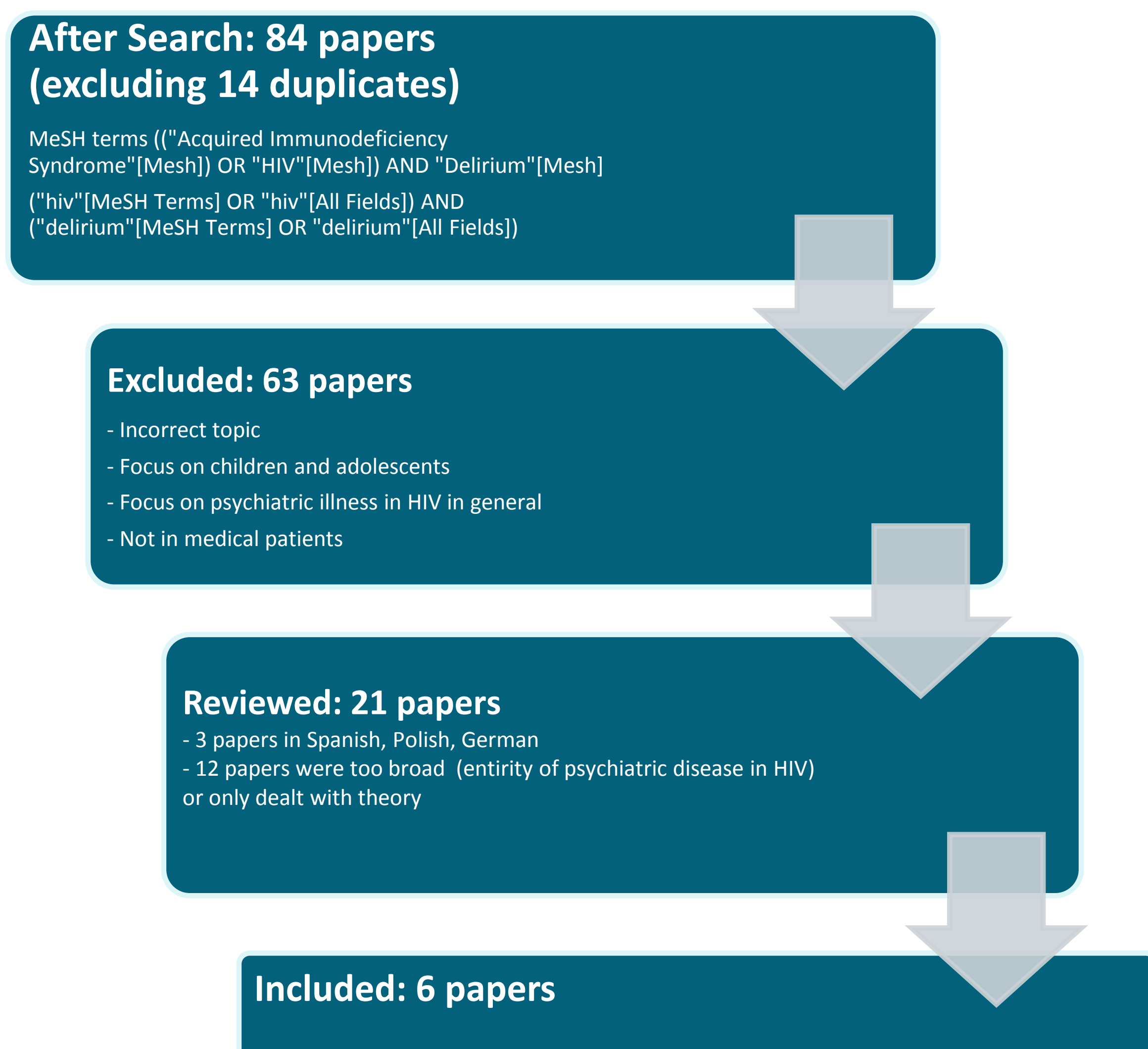
Objectives of the literature Review

We aimed to identify the published prevalence, the risk factors for and the outcomes of delirium in HIV positive patients with a focus on hospitalised patients in countries with a high HIV prevalence.

Literature Search Strategy

An overview of contemporary literature (up to 28 February 2018) was undertaken through a comprehensive search strategy on academic literature databases to which the University of Cape Town subscribes (Pubmed, EBSCO host (CINAHL, Academic Search Premier, African-wide Information), Cochrane and Medline). More information regarding the search strategy and prioritisation can be found in the flow diagram below:

Figure 1: Research flow diagram



Delirium in HIV

Prevalence

There are very few studies that specifically review delirium in HIV positive patients but the prevalence rates are 12-57%, and almost all of these studies are in the pre-ART era.(59-64) One study based in Paris found that delirium was the most common neurological complication (45%) of HIV positive patients admitted to ICU.(65) A study in Texas looking at medical inpatients with HIV referred to psychiatric liaison services found that 57% of the referred patients had delirium; of these patients 55% had delirium, 36% had delirium and dementia, and 9% had delirium an addition to another organic mental disorder (OMD).(64) A retrospective chart review in a Washington specialist HIV nursing facility, found that delirium was poorly diagnosed and reported, and that this could account for the variable rates of reported delirium in HIV positive patients.(62) Of the 137 charts reviewed only 1 patient was recorded as having delirium, whereas the chart review found 64 patients (46%) had delirium based on a retrospective CAM. Three studies by Uldall *et al.*(59-61) in 1994 and 1996 assessed the outcomes for HIV positive delirious patients in an assisted living centre and an American teaching hospital respectively. These studies had small sample sizes but two used formal testing with the CAM to assess for delirium. Delirium was present in 12% - 46% of patients in these three studies.(59-61) . However, all these studies took place before the implementation of combined ART therapy and prophylaxis for opportunistic infections (OIs) which may mitigate the mortality in an environment with broad ARV coverage and OI prophylaxis.(66, 67) There is little available data with regards to prevalence, risk factors for, or outcomes of delirium amongst persons living with HIV in the post-ART era.

Risk factors

Very little is known concerning specific risk factors for delirium in the HIV positive population. One of the psychiatric liaison studies found that a cause could be found for only 68% of HIV positive patients with delirium. The most common causes were CNS infections (toxoplasmosis, cryptococcal meningitis, and herpes encephalitis), lymphoma, sepsis, metabolic encephalopathy, and patients who had both sepsis and metabolic encephalopathy.(64) Lalonde *et al.* similarly found the most common predictors of delirium in HIV positive cohort were: medication side effects (48%), fever (38%), and infection (20%).(62) This was again similar to another study that found associated medical conditions included: medication changes (44%), fever (38%), and infection (26%). This study also found that the presence of HIV related illness did not significantly contribute to delirium.(59) Uldall *et al.* found no specific risk factors for delirium in HIV positive patients apart from being prescribed ≥3 CNS active medications and that benzodiazepine and narcotic use were significantly associated with delirium; this is in keeping with a prospective cohort study by Inouye *et al.*, where polypharmacy (the use of, or addition of, greater than three medications) was associated with an increase in incident delirium [RR 2.9 (95% CI, 1.6 to 5.4)].(43, 59, 60, 68) Uldall *et al.* also found that a low CD4 count was not predictive of delirium.(60)

HIV neurocognitive impairment (NCI) is a subcortical dementia characterised by behavioural changes, memory deficit, and psychomotor slowing.(69-71) Patients with cognitive dysfunction, especially dementia, are at a higher risk of delirium.(13) The severity of HIV NCI is related to the number of activated CNS macrophages, and the release of macrocyte and astrocyte derived products.(69-71) In a recent meta-analysis Habib *et al.*(72) reviewed NCI in HIV-1 infected individuals in Sub-Saharan Africa (SSA). The review looked at 16 studies from seven countries and showed a combined odds ratio of 6.49 (95% CI 1.68–25.08)

for NCI in HIV positive patients as compared to HIV negative controls. The estimates of NCI in adults pre-Anti-Retroviral Therapy (ART) was 42.4 % (95%CI: 32.2–52.6 %) while the estimate for adults on ART for greater than six months was 30.4 % (95 % CI: 13.2–47.6 %).(72) Comparatively, NCI rates in the pre-ART era in the USA were 15-20%.(73) This meta-analysis attributed the higher incidence of HIV NCI in its population to the fact that patients in SSA have lower performance scores, and typically present later with profound immunosuppression. These patients also have a higher incidence of opportunistic infections and anaemia.(72) Risk factors for HIV NCI include advancing age, high HIV viral load (VL) early in infection, low CD4 counts, low body mass index, anaemia, female gender, and injection drug use.(69) As neurocognitive impairment is a well described risk factor for delirium, it is not surprising that studies have shown high, but variable, prevalence rates of delirium in the HIV positive population of between 3.7-57%.(37, 62-64) Furthermore, 8-22% of cases present with concurrent NCI.(60, 61, 72, 74)

Prognosis

In two studies, Uldall *et al.* found that HIV positive patients with delirium had significantly longer hospital stays and were more likely to need specialised care if discharged alive. These patients had higher rates of mortality than those without delirium, and that delirium was an independent marker of inpatient mortality in HIV positive patients with a mortality rate of 63% and 97% respectively.(59, 60) Fernandez *et al.* found that in their selected study group 50% of HIV positive patients with delirium had only partially reversible delirium while 13% progressed to a more chronic OMD (the most common being dementia). However, even the HIV positive patients with fully reversible delirium had behavioural and cognitive abnormalities after resolution.(64)

Conclusion

South Africa has a high prevalence of HIV and non-communicable diseases, in a region with high rates of delirium. This population is therefore at risk of the complications associated with delirium, including increased morbidity, increased mortality, and greater costs to the health system. It is important to establish an awareness of risk factors in this is population to allow early identification and prevention of delirium. An extensive literature review showed that there is no data pertaining to this high risk group of patients.

Aims and Objectives of the Study:

Aim:

To identify the prevalence, risk factors, and outcomes of delirium in HIV infected individuals admitted to South African hospitals.

Objectives:

1. To identify the prevalence of HIV in patients admitted to medical wards, using a gold standard and validated Questionnaire.
2. To assess potential risk factors for delirium, including demographic data, disease status, admission diagnoses, medication and laboratory data.
3. To assess the short and medium term mortality rates of HIV patients admitted with delirium versus those without.

(Word count: 3550)

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Chapter Two: Manuscript

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

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Research in context

Evidence before this study

We searched PubMed and Medline for articles up to 28 February 2018, using the search terms: “delirium”, “HIV”, “mortality”, “risk factors”, “Sub-Saharan Africa (SAA)”, and “South Africa”. The majority of published delirium research is confined to HIV uninfected, geriatric populations in developed countries. In the one systematic review of delirium in SSA only one paper focussed on delirium, most of the patients were not tested for HIV, no standard criteria was used for delirium diagnosis; and cohorts were restricted to paediatric/adolescent, psychiatric, and ICU populations. Published data on delirium in HIV infected patients are few, restricted to developed countries or prior to widespread uptake of combination antiretroviral therapy (ART).

Added value of this study

This is the first study of delirium, diagnosed with validated reference testing, in HIV-infected acute medical admissions from a setting with good uptake of ART. In contrast to geriatric populations from developed settings, this is a young patient cohort from South Africa - a developing country with high burdens of HIV, tuberculosis (TB), and non-communicable diseases (NCDs). In this setting, delirium was common and an independent risk factor for inpatient mortality in HIV positive patients. Amongst HIV-infected admissions, advancing age and uraemia were the main delirium risk factors, while the use of ART at admission was protective. Traditional markers of advanced immunosuppression (low CD4 cell count and unsuppressed HIV viral load) and active TB did not increase risk for delirium.

Implications of all available evidence

Delirium is common and an important independent predictor of poor outcome in HIV infected acute medical admissions. Older HIV-infected patients with renal dysfunction are at high risk for admission with acute delirium, while those using ART on admission are protected.

Abstract (240/250)

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

Methods
Three cohorts of adult acute medical admissions to Groote Schuur and Victoria Hospitals, Cape Town, South Africa 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 (CAM).

Findings
The study included 1182 acute medical admissions; with 318 (26·9%) HIV-infected. Median(IQR) age and CD4 count was 35(30-43) years and 132(61-256) cells/mm3 respectively, with 140/318(44%) using ART on admission. Delirium prevalence was 17·6%(95% CI 13·7-22·1%) amongst HIV-infected patients and was an independent risk factor for inpatient mortality. In multivariable logistic regression, factors associated with delirium were age ≥55 years(AOR 6·95[2·03-23·67], p=0·002) and urea ≥15(AOR 4·83[1·7-13·44], p=0·003), while ART use reduced risk (p=0·014). Low CD4 count, unsuppressed viral load, and active TB were not predictors of delirium; nor were other traditional risk factors such as non-opportunistic, acute infections or polypharmacy.

Interpretation
Delirium is common and predicts poor outcome in HIV-infected acute medical admissions in endemic settings despite increased ART use. Older HIV-infected patients with renal dysfunction are at high risk for inpatient delirium while those using ART on admission are protected.

Introduction

The prevalence of delirium in acute medical in-patients is high, with estimates ranging from 10-31%.[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, this extensive published data on delirium outcomes and risk factors in general medical in-patients comes almost exclusively from geriatric populations in developed countries, a very different population to acute medical admissions in developing country settings with high HIV/TB burden.[5] Furthermore, the few studies from developing country settings like Sub-Saharan Africa (SSA) have either been conducted in medical patients >60 years or in specialised populations, such as psychiatric and intensive care settings.[6-8] In developed countries studies have been done amongst HIV-infected populations before universal access to combination anti-retroviral therapy (ART) in the United States.[9-14]

HIV targets the 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. Thus, it is unsurprising that studies have shown high prevalence rates of delirium (3·7-57%) in the HIV-infected population. [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, thus widespread access may mitigate delirium risk. Therefore, it is unclear amongst acute general admissions in HIV endemic settings with universal ART programmes, if HIV infection remains an independent risk for delirium.[9] Furthermore, in developing country settings with high burdens of communicable (CD) and non-communicable diseases (NCD), like South Africa, clinicians do not know which delirium risk factors to identify amongst HIV-infected admissions. Available data is almost exclusively from before universal ART access;[9-13,16] furthermore, data from SSA populations is highly variable, due to a lack of standardised delirium testing methods, or incomplete HIV testing.[6] We aimed to conduct a study amongst acute medical admissions with high HIV burden using standardised delirium diagnostic testing methods in a country with universal access to ART.

Methods

Study design and participants

This prospective cohort study focused on HIV-infected acute general medical admissions, and was a planned analysis within a parent prospective randomised cohort study designed for the development and validation of a novel four-question delirium screening tool, however this study used the Confusion Assessment Method (CAM) reference testing. A computer generated, random selection of daily acute general medical admissions to two hospitals (Groote Schuur (GSH) and Victoria (VWH)) in Cape Town, South Africa, 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 ≥18 years admitted on weekdays were eligible; and a random sample of ten patients per day were selected (usual daily patient intake 15-25 patients), to allow study staff to perform delirium testing within 24 hours of admission. Exclusion criteria included: i) Informed consent declined; ii) Age <18 years; iii) Glascow Coma Score ≤12; and iii) Aphasia (Figure 1).

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 again to the patient and written informed consent was taken. If this was not possible as part of the initial in-patient admission, then 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 then the HREC granted a waiver to allow the inclusion of patient data. The study was approved by the University of Cape Town Human Research Ethics Committee (HREC).

Delirium testing

Within 24 hours of admission, a study physician reviewed the patient's charts and gathered information pertaining to the patient's primary diagnosis, clinical background, admission medication, level of education, and demographic information. An independent study physician trained in delirium testing (in the development study) or 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 precence of language barriers was noted (see Figure 1)and a ward based translator was used, when possible, so that testing was performed in the patients' first language.

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, any patients that refused HIV testing during this admission were excluded from the study. A positive HIV status was defined as any record of a positive HIV test (either rapid or ELISA) at any point prior to or during index admission dating back to January 2005 (the earliest available information on the National Health Laboratory results

electronic system). The CD4 count and HIV viral load (VL) most proximal 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 ICD 10 codes. We analysed the association of delirium with the top five most frequent CDs and NCDs; while 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 Medical Formulary. Antiretrovirals (ARVs), anti-TB medication, and the medication for prophylaxis of OIs (Fluconazole and Trimethoprim/sulfamethoxazole) were assessed as possible protective factors for delirium in HIV-infected patients. Detailed information on ICD10 and medication groupings is provided in the online supplementary data. Outcome mortality data was obtained from patient folders, 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 (Stata Corp., College Station, TX). Continuous variables were summarized as frequencies and percentages and categorical variables as medians with inter-quartile range (IQR). Socio-demographic, clinical characteristics and outcomes were assessed for differences between HIV-infected, HIV-uninfected, and HIV unknown patients overall; and restricted to those with delirium. Analysis was then restricted to HIV-positive patients to compare socio-demographics, clinical characteristics and outcomes between cases with and without delirium. Associations between categorical variables were analysed using chi-square test and Fisher's exact, as appropriate. Wilcoxon rank-sum or Kruskal-Wallis test was used for comparison of continuous variables between two and three groups respectively.

Univariable and multivariable logistic regression was performed to identify risk factors for delirium in HIV-infected patients. Variables analysed in univariable analysis were considered *a priori,* and 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 ($p < 0{\cdot}05$). Education >7 years and CD4 count were retained in the multivariable model regardless of significance due to their clinical relevance. Odds ratios (OR) were reported with 95% confidence intervals (95% CIs). A $p<0{\cdot}05$ was interpreted as statistically significant.

Results

A total of 1565 patients were randomised to the parent study (459 and 1106 in the development and validation phases respectively) (Figure 1). Of these, 383 were excluded and a total of 1182 patients considered as part of this analysis. The prevalence of HIV-infection was 26·9%(318/1182); with 44%(140/318) using ART on admission. Table 1 and Table 2 describes the cohort stratified by HIV status and then restricted to only patients with delirium. Overall, the median (IQR) age was 49·5(34-63·2) years, and 53·1% were female. HIV-infected patients were younger than both HIV-uninfected and unknown [35(30-43) years vs. 52·7(38-64·7) years and 66(55·5-75·3) years, p=0·0001). The median(IQR) CD4 count was 132(61-256) cells/mm^3. Delirium prevalence was 17·6%(56/318) in HIV-infected patients (p=0·161). Overall inpatient and 12-month mortality was 6·2%(72/1182) and 23·8%(281/1182), with no difference by HIV status. There was no loss to follow up in either inpatient or 12-month mortality. Amongst HIV positive patients, delirium was an independent predictor of inpatient mortality (14·6% vs 5·4%, p=0·036), but though HIV infected patients had a higher 12-month mortality the result was not significantly different (33·9% vs 22·9%, p=0·083 respectively).

Table 1 and Table 2 show primary admission diagnoses, key laboratory parameters and the five commonest admission medications. NCDs accounted for more hospital admissions than CDs (69·7% vs 27·8%, p<0·0001) and two distinct patient groups are evident. HIV-infected patients had low rates of NCDs, and a high burden of TB and other CDs, such as meningitis/encephalitis. HIV patients used more medication (15·1% on ≥three medications), due 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 NSAIDS and cardiac drug prescribing was higher than in HIV positive patients (p<0·0001). These differences were present in comparing the overall patient population and when restricted to patients with delirium. This shows that HIV infected patients have an unique profile relative to HIV-uninfected general medical admisions.

HIV-infected patients are compared in Table 3 by the presence or absence of delirium. The two groups are 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[95% CI: 32-214] vs 150[95% CI: 62-266], p=0·1284), and lower rates of HIV viral suppression (27·3% vs 40%, p=0·519), no statistically significant differences were found. However, the delirium group had significantly lower Hb (p=0·0194), higher urea (p=0·0047), and creatinine (p=0·0197). A higher number of patients without delirium were using ≥ three admission medications (45[17·2%] vs 3[5·4%], p=0·023) with a greater number of patients on ARVs, antibiotics, and OI prophylaxis (Sulfamethoxazole / Trimethoprim and Fluconazole). However, use of TB medication was similar between the two groups (19·6% vs 19·5%, p=0·976).

Table 4 shows the univariable and multivariable logistic regression analysis exploring protective and risk factors for prevalent delirium in HIV-infected acute medical admissions. For every five year increase in age there is a 25% increased risk of delirium (95% CI: 1·1-1·5 p=0·008), with an AOR of 6·95(2·03-23·67) using an ROC-selected age ≥55 (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 ≥15mmol/l increased the risk of delirium, with only urea

≥15mmol/l retained in the multivariable analysis (AOR 4·83[95%CI: 1·7-13·44], p=0·0003). Patients using ≥three 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

Delirium is a well-established predictor of poor outcomes, both short and long-term, and attendant healthcare costs are substantial. However, the overwhelming majority of all aspects of published delirium data are concentrated either on specialised populations e.g. ICUs or geriatric settings with a median age >65 years.[1,6,19] Available data from developing country settings are highly variable, often lacking standardised delirium testing methods or HIV testing and treatment data.[6] Focussed HIV delirium studies also either come from specialised care settings (e.g. psychiatry) or have been conducted prior to universal access to ART.[9-14,20] Yet, the majority of in-patient care in health systems worldwide is delivered in medical wards; in developing HIV-endemic settings mostly in undifferentiated general medical wards Our study is the first to study delirium, using a validated testing method, amongst HIV infected inpatients, admitted in the context of an acute general medical intake in a developing country with dual CD and NCD burdens[5], and in the setting of improved access to ART. The key findings of our study include: i) Delirium occurs 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 of inpatient mortality amongst 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 amongst 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.

Despite ART coverage of 44% amongst acute HIV-infected medical admissions, the prevalence of delirium is high amongst HIV-infected patients. Furthermore, delirium is an independent predictor of increased inpatient mortality. Our cohort delirium prevalence of 17·6% is consistent with both the 4-30% and 12-57% prevalence figures published in a recent review on delirium in SSA[6], and American studies[12-15,21] in HIV-infected medical inpatients respectively. No data are available on HIV-infected medical inpatients in the ART era. Studies show that in general medical wards delirium goes undiagnosed in 32-67% of patients and that this group of patients has a higher mortality rate.[22] Lalonde et al found that only one of 46 HIV-infected patients was correctly diagnosed with delirium in a specialist HIV center.[11] 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 for example, NICE recommends risk factor and indicator assessment for all patients admitted to hospital,[23] and incident delirium is used as a marker of good clinical governance.[24] No rapid delirium screening tools have been validated in a developing country setting where patients are younger and consequently have lower co-morbid dementia rates– this is an obvious gap.

Older HIV-infected patients with acute renal dysfunction are at high risk for inpatient delirium while those using ART on admission seem to be protected. The protective effect of ART on delirium risk is not surprising, given its known benefit on the neurocognitive impairment associated with HIV.[25] Similarly, we found three known delirium risk factors to be important in our HIV-infected patients on univariable analysis: increasing 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] However, in our cohort many typical risk factors: acute non-oppurtunistic infections, 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 is most likely attributable to the pill burden of combined ART and requirement for OI antibiotic prophylaxis in HIV-infected patients. This finding is clearly in 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 that found the use of ≥ three CNS active medications and medication side effects were key risk factors for delirium.[9,11] , Medications that significantly contributed to delirium in another study were benzodiazepines and narcotics,[21] this was also not found in our study. Notably, all studies were in the pre-combination ART era and use was not reported.

This study is the largest study to conduct formalised delirium testing in HIV-infected acute medical admissions. Nevertheless, despite this large overall study size, there were only 56 cases of delirium amongst the HIV-infected group. Thus, we had limited power to detect small differences between groups, and regression analysis findings should be interpreted cautiously. 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 a concern about possible inclusion bias. Fortunately, only ~13% of patients were HIV unknown out of a large cohort, and there was very little missing CD4 cell count data. The HIV unknown cohort was a group of older patients with more NCDs, less infections, and less TB, likely thought by attending clinicians to be low risk for HIV infection. Although, assessing prevalent delirium on admission may be difficult due 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.

Delirium is common, poorly recognised, and has high morbidity and mortality with significant costs for health care systems.[3] We have shown that even with improved ART coverage, delirium is common and an independent predictor of mortality in HIV-infected patients in a developing country setting with a dual burden of HIV and TB, as well as a growing burden of NCDs. Clinicians need to be aware that aging 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 viral load does not likely increase the risk of delirium. Further delirium research using standardised testing method is required to validate these findings in other developing countries.

Contributors and roles

JP designed and led the development study. JP and PR designed and led the validation study. FA and CD enrolled patients and collected data for the validation study. CD, FA, NV, and CA entered and collated the original data. CD and JP designed and wrote the study protocol. CD and KM analysed and interpreted data. CD wrote the first draft of the report and all authors reviewed and approved the final version.

Declaration of interests

We declare no competing interests.

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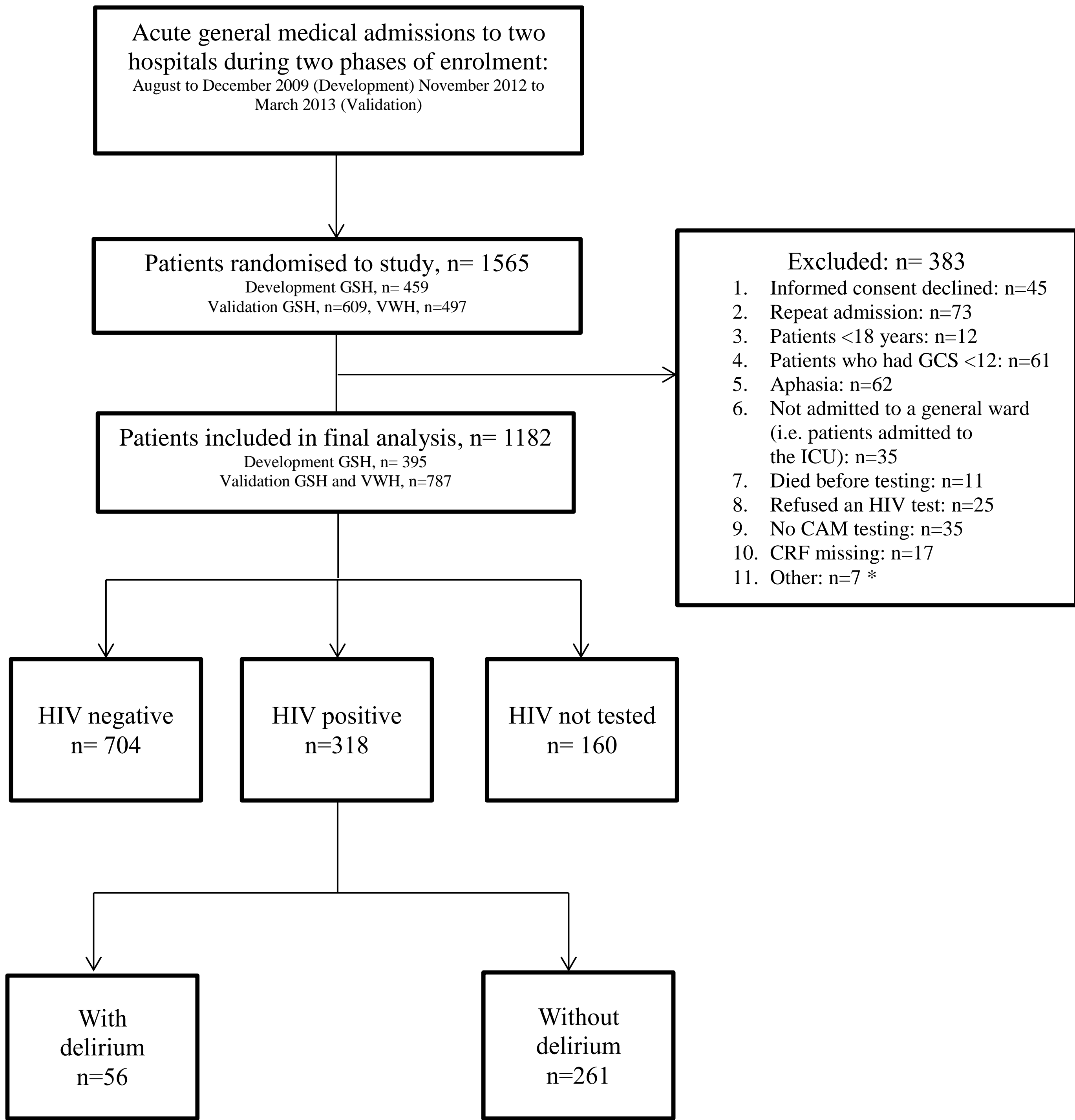
Appendix 4: Univariable analysis of risk factors for delirium in HIV-infected patients



*Other: n=7 (Language barrier, deaf, elective admission)

CAM: Confusion Assessment Method, CRF: Case Report Form, GSH: Groote Schuur Hospital, HIV: Human Immunodeficiency Virus, VWH: Victoria Wynberg Hospital

Figure 1: Consort diagram

	All (n=1182)	HIV-infected (n=318)	HIV-uninfected (n=704)	HIV not tested (n=160)	P value
Age in years, med(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(62)	335(47·6)	95(59·4)	<0·0001
Education ≥7 years, n(%)	830(75·9)	230(79)	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(%)[1], n=1153					
Non-communicable disease (NCD) 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)	11(3·5)	72(10·2)	11(6·9)	0·001
- Cerebrovascular	70(5·9)	4(1·3)	49(7)	17(10·6)	<0·0001
- Renal failure	42(3·6)	9(2·8)	30(4·3)	3(1·9)	0·293
Communicable disease (CD) 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,med(IQR)					
- WCC, n=1124	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, n=1122	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, n=1102	138(135-141)	135(132-139)	139(135-141)	140(138-143)	0·0001
- Urea, n=1101	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					
Absolute number of medication ≥3	90(7·6)	48(15·1)	28(4)	14(8·8)	<0·0001
5 most common admission medications, n(%) [2]					
- 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 medication	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(%)					
- In-patient	72(6·2)	22(7)	40(5·8)	10(6·3)	0·7540
- 12 months	281(23·8)	79(24·8)	167(23·7)	35(21·9)	0·7710

[1] See **Appendix 1** for detailed diagnoses
[2] See **Appendix 2** for details of medications

CD: communicable disease, CVS: cardiovascular system, Hb: Haemoglobin, HIV: Human Immunodeficiency Virus, IQR: Inter-quartile range, NCD: non-communicable disease, NSAIDs: Nonsteroidal anti-inflammatory, TB: Tuberculosis, UTI: urinary tract infection, WCC: white cell count

Table 1: Comparison of HIV-infected, HIV-uninfected and HIV unknown populations

	All patients with delirium (n=172)	HIV-infected with delirium (n=56)	HIV-uninfected with delirium (n=97)	HIV unknown with delirium (n=19)	P value
Age in years, med(IQR)	53(37-66·5)	34·5(30-45)	57(46-69)	76(61-82)	0·0001
Female, n(%)	87(50·6)	33(58·9)	43(44·3)	11(57·9)	0·175
Education ≥7 years, n(%)	82(67·8)	28(73·7)	44(63·8)	10(71·4)	0·565
Dementia/cognitive deficit, n(%)	17(9·9)	3(5·4)	8(8·3)	6(31·6)	0·009
Primary diagnosis: n(%)[1], n=167					
Non-communicable disease (NCD) total	112(65·1)	23(41·1)	75(77·3)	14(73·7)	0·000
4 most common NCDs					
- Cerebrovascular	16(9·3)	0(0·0)	14(14·4)	2(10·5)	0·003
- CVS	16(9·3)	2(3·6)	13(13·4)	1(5·26)	0·105
- Renal failure	11(6·4)	5(8·9)	6(6·2)	0(0·0)	0·432
- Encephalopathy	5(2·9)	2(3·4)	3(3·1)	0(0·0)	1·000
Communicable disease (CD) total	55(32)	28(50·0)	22(22·7)	5(32)	0·002
3 most common CDs[1]					
- TB total	25(14·5)	16(28·6)	9(9·3)	0(0·0)	0·001
- Pulmonary TB	12(7)	5(8·9)	7(7·2)	0(0·0)	0·562
- TB meningitis	6(3·5)	4(7·1)	2(2·1)	0(0·0)	0·287
- Disseminated TB	7(4·1)	7(12·5)	0(0·0)	0(0·0)	0·001
- Pneumonia	13(7·6)	7(12·5)	4(4·1)	2(10·5)	0·123
- UTI	7(4·1)	0(0·0)	5(5·2)	2(10·5)	0·067
Laboratory results, med(IQR)					
- WCC, n=169	9(6·7-12·4)	8·3(5·9-9·7)	9·4(8-13·6)	9·1(5·8-12·5)	0·0154
- Hb, n=169	10·1(9-12·8)	9·5(8·1-10·3)	11·1(9·5-13·7)	10·6(9·7-13·8)	0·0001
- Sodium, n=167	138(132-143)	134·5(131-140)	139(135-143)	142(137-150)	0·0003
- Urea, n=166	8·6(5·5-23·4)	7·2(4·5-16·7)	9·4(6-25·2)	9·8(8·2-26·3)	0·0666
Medication					
Absolute number of medication ≥3	11(6·4)	3(5·4)	66·2)	2(10·5)	0·739
5 most common admission medications, n(%)					
- NSAIDs	29(16·9)	0(0·0)	19(19·6)	10(52·6)	0·000
- Cardiac	23(13·4)	0(0·0)	18(18·6)	5(26·3)	0·000
- TB medication	18(10·5)	11(19·6)	7(7·2)	0(0·0)	0·024
- Mood stabilisers	11(6·4)	3(5·4)	8(8·3)	0(0·0)	0·489
- Antipsychotics	7(4·1)	0(0·0)	5(5·15)	2(10·2)	0·067
Mortality, n(%)					
- In-patient	26(15·6)	8(14·6)	14(15·1)	4(21·1)	0·710
- 12 months	65(37·8)	19(33·9)	37(38·1)	9(47·4)	0·582

[1] All other diagnoses < 3%

CD: communicable disease, Hb: haemoglobin, IQR: inter quartile range, Med: median, NCD: non-communicable disease, NSAIDs: non steroidal anti-inflammatory drugs TB: tuberculosis, UTI: urinary tract infection, WCC: white cell count,

Table 2: Comparison of HIV-infected, HIV-uninfected and HIV unknown populations with delirium

	HIV-infected with delirium n=56	HIV-infected without delirium n=261	P value
Age in years, med(IQR)	34(30-43·1)	34·6(29·4-41·7)	0·373
Female, n(%)	33(58·9)	164(62·6)	0·608
Education ≥ 7years, n(%)	28(73·7)	202(79·8)	0·385
Primary diagnosis: n(%)[1], n=337[2]			
Non-communicable total	23(41·2)	118(45·0)	0·588
4 most common NCDs			
- CVS combined	2(3·6)	27(10·3)[7]	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)	114(43·5)	0·375
4 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
- Meningitis / Encephalitis	2(3·6)	9(3·4)	1·000
- Sepsis	0	3(1·2)	1·000
HIV specific diagnoses, n(%) [3]	10(17·9)	44(16·8)	0·847
3 most common[4]			
- CCM	3(5·4)	8(3·1)	0·417
- PJP	0	8(3·1)	0·359
- HAND	4(7·14)	6(2·29)	0·079
Laboratory results, med(IQR)			
- CD4, n=302	104(32-214)	150(62-266)	0·1284
- Viral suppression[5], n=86	3(27·3)	30(40)	0·519
- WCC, n=309	8·3(5·9-9·7)	8(5·7-9·5)	0·6299
- Hb, n=308	9·5(8·1-10·3)	9·8(8·7-12·1)	0·0194
- Sodium, n=297	134·5(131-140)	135(132-139)	0·3279
- Urea, n=297	7·2(4·5-16·7)	5·7(3·9-8·5)	0·0047
- Creatinine, n=306	83(65-208)	76(58-94)	0·0197
- CRP, n=185	76·2(28·9-135·2)	45·7(20-107·1)	0·3522
Admission Medication, n(%) [6]			
- Absolute number of medication ≥3	3(5·4)	45(17·2)	0·023
- ARVs	14(25)	126(48·1)	0·002
- Sulfamethoxazole / Trimethoprim	3(5·4)	38(14·5)	0·078
- Fluconazole	0	7(2·7)	0·611
- TB medication	11(19·6)	51(19·5)	0·976
- Antibiotics	4(7·1)	45(17·2)	0·067
Mortality, n(%)			
- In-patient	8(14·6)	14(5·4)	0·036
- 12 months	19(33·9)	60(22·9)	0·083

[1] See **Appendix 1** for detailed diagnoses
[3] See **Appendix 3** for details of HIV specific diagnoses
[2]19 patients had dual primary diagnoses i·e· CCM and Pulmonary TB
[4]All other diagnoses <3%
[5]Lower than detectable limit or <20 RNA copies /million
[6] See **Appendix 2** for details of medication
[7]The diagnoses in this group were: venous thromboembolic disease (29·6%) and cardiac failure (29·6%), cardiomyopathy (11·1%) and pericarditis (11·3%)·

ARVs: Anti-Retroviral, CCM: Cryptococcal meningitis, CD: communicable disease, CRP: C-reactive protein, CVS: cardiovascular system, Hb: haemoglobin, HIV: Human Immunodeficiency Virus, IQR: inter-quartile range, NCD: non-communicable disease, NSAIDs: nonsteroidal anti-inflammatory drugs, PJP: *Pneumocystis jerovici* pneumonia, TB: tuberculosis, UTI: urinary tract infection, WCC: white cell count

Table 3: Comparison of HIV-infected population with and without delirium

Variable	Univariable (OR, 95% CI)	P value	Multivariable (AOR, 95% CI)	P value
Age(five 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 continuous[1]	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(1-1·1)	0·008		
- Urea ≥15	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

[1]Logarithmic analysis in Multivariable models

AOR: Adjusted odds ratio, ARVs: anti-retroviral drugs, CCM: Cryptococcal meningitis, CD: communicable disease, Hb: Haemoglobin, HIV: Human Immunodeficiency Virus, IQR: inter-quartile range, NCD: non-communicable disease, TB: tuberculosis, WCC: white cell count,

Table 4: Univariable and multivariable analysis of risk factors for delirium in HIV-infected patients

Primary diagnosis, n=1207	**n(%)**
Noncommunicable Disease	824(69·7)
CVS combined - Hypertension (HPT) - Ischaemic heart disease (IHD) - Congestive cardiac failure (CCF) - Valvular and nonvalvular heart disease (other than HPT, IHD and CCF) - Venous thromboembolic disease (VTE):Deep vein thrombosis) DVT and Pulmonary Embolism (PE)	238(20·1)
Respiratory combined - Chronic Obstructive Pulmonary disease (COPD) - Asthma - Respiratory disease other than COPD and Asthma e·g· Interstitial lung disease	94(8)
Cerebrovascular - Ischaemic and haemorrhagic stroke - Intracranial bleed	70(5·9)
Renal failure: Acute and chronic	42(3·6)
Fluid / electrolyte imbalances	16(1·4)
Delirium/encephalopathy	14(1·2)
Liver failure	12(1)
Other	338(28·6)
- Cancer - Non- cerebrovascular disease neurological disease e·g· CIPD, peripheral neuropathy - Endocrine disorders e·g· Hypo/hyperthyroidism, Diabetes Mellitus (DM) - Renal disease other than AKI and CKD e·g·Nephritic syndrome - Gastrointestinal disease - Rheumatological disease - Psychiatric disease - Haematology - Other e·g· pregnancy, trauma, iatrogenic	
Communicable disease	329(27·8)
- TB total	145(12·3)
- Pulmonary TB	75(6·4)
- TB meningitis	20(1·7)
- Disseminated TB	33(2·8)
- Pneumonia	88(7·5)
- Meningitis / Encephalitis	21(1·8)
- UTI	20(1·7)
- Gastroenteritis	19(1·6)
- Sepsis	12(1)
- Other e·g· Disseminated gonococcosus	29(2·5)

Appendix 1: Primary diagnoses

Group	Medication
Benzodiazepines	Clonazepam Diazepam Lorazepam
Anticholinergics	Ditropan Domperidone Hyoscine butylbromide Ipratropium bromide Orphenadrine Oxybutynin
Dopaminergics	Carbidopa-levodopa Levodopa Methyldopa
Antispasmodics	Metoclopramide
Antihistamines	Cetirizine dihydrochloride Chlorpheniramine Cimetidine Cinnarizine Promethazine Ranitidine
Antipsychotics	Chlorpromazine Clopixol Clozapine Haloperidol Olanzepine Prochlorperazine Quetiapine Risperidone Trifluoperazine
Antidepressants	Amitryptiline Citalopram Duloxetine Fluoxetine Imipramine Mirtazapine Trazodone Venlafaxine
Mood stabilisers	Lithium Sodium valproate
Steroids	Beclomethasone Betamethasone Budesonide Dexamethasone Dovate Fenoterol Formoterol Hydrocortizone Lenovate Prednisolone Prednisone
NSAIDs	Aspirin Diclofenac Ibuprofen
Cardiac Drugs	Amiodarone Furosemide Propranolol
Bronchodilator	Theophylline
Antibiotics	Amikacin Amoxicillin

	Ampicillin Azithromycin Co-Amoxiclav Ceftriaxone Cefuroxime Chloramphenicol Ciprofloxacin Clarithromycin Clindamycin Clofazimine Clotrimazole Cotrimoxazole Dapsone Doxycycline Ertapenem Erythromycin Flucloxacillin Gentamycin Kanamycin Metronidazole Moxifloxacin Ofloxacin Penicillin Penicillin G Penicillin VK Piperacillin/tazobactam Streptomycin Sulfamethoxazole / trimethoprim Vancomycin
Medication as protective factor for delirium in HIV	
Antiretrovirals	Abacavir Atazanvir Efavirenz Emtricatabine Lamivudine Lamivudine / zidovudine Lopinovir / Ritonovir Nevirapine Stavudine Tenofovir Tenofovir / Emtricitabine / Efavirenz Zidovudine
Anti-TB Medication	Ethambutol Ethionamide Isoniazid Kanamycin Moxifloxacin Pyrazinamide Rifampicin Rifampicin/Isoniazid Rifampicin / Pyrazinamide / Isoniazid / Ethambutol Terizidone
CCM prophylaxis	Sulfamethoxazole / trimethoprim
PJP Prophylaxis	Fluconazole

Appendix 2: Medication and grouping used for analysis

HIV Specific Diagnoses, n=54	**Frequency, n(%)**
Cryptococcal Meningitis	11
Pneumocystis jerovici pneumonia	8
Kaposi's sarcoma	3
Progressive multifocal leukoencephalopathy (*PML*)	1
Toxoplasmosis	1
Cytomegalovirus (CMV)	3
Histoplasmosis	2
Isopora	2
Cryptosporidiosis	1
Dementia in HIV	10
Immune reconstitution inflammatory syndrome (IRIS)	2
HIV not specified	10

Appendix 3: Frequency of HIV specific, primary and secondary diagnoses

	Univariable (OR, 95% CI)	P value
Age(five year increase)	1·12 (0·99-1·3)	0·065
Age ≥55 years	4·1 (1·6-11·1)	<0·0001
Education (≥7 years)	0·71 (0·3-1·6)	0·386
HIV specific diagnosis		
- CCM	1·8 (0·5-7)	0·398
Primary diagnosis		
Non-communicable (NCD)		
- Renal failure	6·3(1·6-24·4)	0·007
Communicable (CD)		
Infection and TB composite	1·30(0·73-2·31)	0·376
TB composite	1·2(0·6-2·2)	0·56
- Disseminated TB	1·6(0·7-4)	0·286
- TB meningitis	1·8(0·5-5·7)	0·351
Infection composite excluding TB	1·2(0·6-2·6)	0·599
- Pneumonia	1·7(0·7-4·3)	0·24
- Meningitis	1·0(025)	0·96
Laboratory values		
- Viral Suppression[1]	0·6(0·1-2·3)	0·422
- CD4 continuous[2]	0·99(0·99-1)	0·241
- WCC	1(1-1)	0·931
- Hb	0·9(0·8-0·98)	0·025
- Sodium	0·98(0·9-1·1)	0·439
- Urea[2]	1(1-1·1)	0·008
- Urea ≥15	5·0 (2·3-10·7)	<0·0001
- Creatinine	1(1-1)	0·002
Medications		
- Total Medication	0·6(0·5-0·9)	0·004
- Absolute number of medications ≥3	0·3(0·1-0·9)	0·035
- ARVs	0·4(0·2-0·7)	0·002
- TB medication	1(0·5-2·1)	0·976
- Sulfamethoxazole / Trimethoprim	0·3(0·1-1·1)	0·076
- Antibiotics	0·4(0·1-1·1)	0·068

[1] Lower than detectable limit or <20 RNA copies /million

Appendix 4: Univariable of risk factors for delirium in HIV-infected patients

Appendices

Appendix 1: RECALL STUDY CONSENT

Acute cognitive dysfunction: short- and long-term outcomes following hospitalisation for general medical illness in Cape Town, South Africa

RECALL-CT Study Patient Informed Consent Form

This research study is about patients who present to hospital with an acute general medical illness and possible confusion. You are invited to participate because you fall into this category.

The purpose of the study is to find out whether

1) a simple 4-question test can diagnose acute confusion in people soon after being admitted to hospital, compared with longer tests that take 20-30 minutes to complete and must be performed by a very experienced doctor; and

2) Whether a more intensive medical follow-up period after discharge from hospital will improve health outcomes in the 12 months after leaving the hospital. Currently it is unknown whether the short-form diagnostic test is effective and whether more intensive follow-up will be better than current practice.

This study has been approved by the UCT FHS Human Research Ethics Committee.

Inclusion criteria

Patient admitted to a general medical ward (including within hospital transfer e.g. ICU discharge)

>18 years and willing and able to give informed consent

Exclusion criteria

Patient admitted directly to the intensive care unit

Patient refusing consent or <18 years old

Aphasic patients unable to speak and undergo cognitive testing

Scientific Importance and Need of the Study

In medical wards, because of high demand, doctors have limited time with each individual patient. This makes the need for quick diagnosis and treatment of acutely ill patients with possible confusion important. Confusion associated with acute medical illness is a serious problem that should receive early attention. Tools are needed to diagnose and manage patients with confusion. This study will investigate whether a particular diagnostic tool is effective and quick and whether an affordable and sustainable package of medical intervention after hospital discharge can improve patient outcomes.

If you agree to join this study project, you will be requested to do the following:

A doctor will complete a special "4-RACY" delirium questionnaire with you, by asking you four easy questions

Within 24 hours, a different doctor will complete another standardised delirium questionnaire, which is a little longer (20-30 minutes), to see how the results compare with those from the 1st questionnaire

After discharge from hospital, you may be contacted telephonically over the next 12-months to enquire about your progress and to remind you about your medical follow-up

You may be requested to attend a medical check-up at your local hospital shortly after hospital discharge

Benefits

You may not benefit directly from participation in the study but we would be grateful for your assistance to help develop a better diagnostic tool and process.

Risks and discomfort

The risk of harm flowing from being involved in this study is minimal.

Any clinical complications arising from your participation in this study will be managed as required and covered by the UCT no fault insurance policy.

Incentive and payment

There is no money incentive or payment for participation in the study

Refusal to participate or withdrawal from the study

The decision to participate is voluntary; you are not forced to participate. You may choose not to participate; you may also decide to withdraw at any time without any penalty. You do not have to explain why you do not wish to participate.

If, after testing the study team feels that you are confused and therefore unable to provide us with informed consent, we will ask permission from a person eligible to give us proxy consent on your behalf. We will then endeavour to consent you when your illness resolves either onsite or telephonically, once you have been discharged.

Confidentiality

All information that you provide will be considered confidential and will not be disclosed to the extent permitted by law. No mention of your name or any other identifying information will emerge on the samples that are drawn or in any publication in connection with this study. Your personal information will NOT be stored with the samples. It is important to note that local hospital personnel who examine your samples could become aware of your name. As a result, the investigators cannot promise total confidentiality, but efforts will be made to maintain confidentiality. No persons other than the research staff and the health workers overseeing your care will have right of entry to any information that identifies you individually. Only the local investigator will have the key to connect the samples and the information attached to your name.

Treatment

We will inform the doctors treating you about the results of our testing for confusion. However, the study team will not make treatment decisions. Your attending medical team will make your medical care and treatment decisions.

We encourage you to ask any questions that you may have and during the study you may contact either the Research Ethics Committee (021 406 6492) or the principal investigator(s) (021 404-9111) if you have further questions

Participant's Statement

I have read the foregoing information/The foregoing information has been read to me. I have had the chance to ask questions about it and any questions that I have asked have been answered to my satisfaction.

I consent voluntarily to take part in this study and I understand that I can withdraw at any time from the study without this in any way affecting my further medical care.

Participant:

Name ____

Signature ______________________________ Date __________________

Or person providing proxy consent:

Name of person providing permission ____

Signature ______________________________ Date __________________

Witness:

Name of the Witness ____

Signature _________________________________ Date ____________________

If initial reference testing diagnosed delirium, and no repeat consent possible:

Patient gives telephonic consent to remain in the study (circle): Yes No Uncontactable

Person taken telephonic consent:

____

Signature _________________________________ Date ____________________

Appendix 2: RECALL STUDY CRF 1

RACY testing: Please complete on Post intake Day

Testing Date	D D M M Y Y Y Y	**Testing Time**	H H : M M		
Completed By (Doctor)	Your Name	**Ran k**	**Intern**	**MO**	**Registrar**

1. Basic Patient Information

USE STICKER if available)		
	First Name:	First Name
	Initials	Middle Name
	Surname:	Surname
	Folder Number:	N N N N N N N N N N
	DOB:	D D M M Y Y Y Y

2. Exclusion Criteria (Do not perform RACY if any answer is YES in Q3)

	Y	**N**
Has this patient electively been admitted? (i.e. Not via casualty, ICU or secondary hospital)		
Is this patient Aphasic?		
Is the patient's Glasgow Coma Scale ≤ 12/15		
Is the patient already discharged/transferred from/out of the acute general medical service?		

3. RACY Delirium Screening Tool

	Question (Ask questions as they are on Sheet)	**Score**
R	Ask Person to **Recognise** 2 people – "Do you know who I am?" Who is this person?(Point to Nurse) (Give 1 point only if patient is able to recognise both people in question)	/1
A	"Can you remember the following **Address** for recall at the end of the test: **No. 42 Strand street**?"	/1

(Ask this question again at the end of question 4)

C **Count** backwards from number 20 to number 1 (No half points, give 1 point if all numbers correct) /1

Y "What is the current **Year**?" /1

Total Score /4

---

4. Communication Barriers Present At Time Of Testing (Tick all that Apply)					
Deafness		Dysphonia		Language Barrier	
Visual Impairment		Dysarthria			

Translator Used for testing?	Y	N

RACY not Completed?	Y	N

5. Chronic Associated Conditions (Diagnosed prior to admission)

Hypertension?	Y N	Year Diagnosed?		Target Organ Damage?	Y	N

Other CVS Dx?	Y N	Year Diagnosed?		Specify ?	

Diabetes?	Y N	Year Diagnosed?		Target Organ Damage?	Y	N

Respiratory Dx?	Y N	Year Diagnosed?		Stage	Mild	Mod	Severe	V Severe

Previous TB?	Y N	Count	N N	Year last diagnosed?	Y Y Y Y		
Fully Treated?	Y N	Regimen ?	1st line	2nd line	MDR	XDR	

Cancer?	Y N	Type?	Organ System(s)	Stage, If known?	Stage

Renal Disease?	Y N	eGFR		Creatinine	

Neuro Disease?	Y N	Year Diagnosed?	

Other Dx?	Y N	Year Diagnosed?		Specify ?	

HIV?	Neg	Pos	Refused	Not Tested	Year Diagnosed	Y Y Y Y	Stage?	1	2	3	4
Latest CD4	count		Unknown	On HAART	Y N	Year Started?	Y Y Y Y				

6. Chronic Medication List (Pre Admission)

	Name of Drug	Dosage	Frequency		Name of Drug	Dosage	Frequency
1				2			
3				4			

5 7 9				6 8 10			
11				12			

7. Discharge Palliative Care Assessment

Would you be surprised if the patient were to die in the next year? **Yes** **No**

Does the patient fulfil any of the following criteria?

Condition	Criteria	TICK
Congestive Cardiac Failure	• Symptoms despite maximal medical therapy • Disabling Shortness of breath at rest (NYHA Class IV) • ≥ 5 Admissions in past 6 months • Other associated organ involvement	
COPD	• Disabling Shortness of breath at rest (NYHA Class IV) • ≥ 5 Admissions in past 6 months	
Renal Failure	• End stage renal disease (GFR <15ml/min) • Not suitable / Declined for dialysis	
Neurological Disease/Stroke	• Severely disabling • Progressive functional decline • Severe dysphagia • Recurrent fever and sepsis	
Frailty / Dementia	• Significant functional impairment • Unable to do ADLs • Incontinence • Recurrent infections	
Cancer	• Stage IV malignancy (Metastatic) • Not for (further) definitive treatment • Spends >50% of time in bed / bedridden	
AIDS	• Stage 3 or 4 disease with dementia • Severe cachexia • Neoplasm, Failure of HAART	
Other	• E.g.: Post cardiopulmonary arrest with CNS damage	

Appendix 3: RECALL STUDY CRF 2

Testing Date	D D M M Y Y Y Y		Testing Time	H H : M M

1.1	Consent (Please Tick)	
Yes	No	Informed consent for Study Participation done? (Please attach Informed Consent Sheet)
Note: If unable to consent Patient – Leave consent sheet in folder – Patient will be consented upon discharge		

1.2 Patient Information

Patient Information **(Please attach sticker if available, otherwise complete)**	**First Name:**	First Name
	Middle Name:	Middle Name
	Surname:	Surname
	Folder Number:	N N N N N N N N N N
	Date of birth:	D D M M Y Y Y Y
Contact Details	**Address:**	House Number, Street Name Suburb Postal Code
	Tel (H) N N N N N N N N N N	**Cell:** N N N N N N N N N N

1.3 Alternate Contact Details (Provide other contact details where patient may be contacted)

Alternate Contact Details 1	**Address:**	House Number, Street Name Suburb Postal Code
	Tel (H) N N N N N N N N N N	**Cell:** N N N N N N N N N N
Alternate Contact Details 2	**Address:**	House Number, Street Name Suburb Postal Code
	Tel (H) N N N N N N N N N N	**Cell:** N N N N N N N N N N
Alternate Contact Details 3	**Address:**	House Number, Street Name Suburb Postal Code
	Tel (H) N N N N N N N N N N	**Cell:** N N N N N N N N N N

2. Barthel Index (Pre-Admission Functioning)

ACTIVITY	SCORE
Feeding 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	0 5 10
Bathing 0 = dependent 5 = independent (or in shower)	0 5
Grooming 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	0 5
Dressing 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	0 5 10
Bowels 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	0 5 10
Bladder 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	0 5 10
Toilet Use 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	0 5 10
Transfers (bed to chair and back) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	0 5 10 15
Mobility (on level surfaces) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	0 5 10 15

Stairs

0 = unable
5 = needs help (verbal, physical, carrying aid)
10 = independent

0 5 10

Total (0 – 100) TOTAL SCORE

3. Reference Testing

3.1 **Exclusion Criteria** (**Don't do any further testing if any answer is YES**)	Y	N
Has this patient refused consent to be part of the Recall CT study?		
Has this patient electively been admitted? (i.e. Not via casualty, ICU or secondary hospital)		
Is this patient Aphasic?		
Is the patient's Glasgow Coma Scale ≤ 12/15		
Is the patient already discharged / transferred from /out of the acute general medical service?		

3.2 Known Risk Factors for Delirium (Please tick all that apply)

Condition	**Y**	**N**
Does the patient's history suggest any pre-existing cognitive impairment, including dementia?		
Is the patient's Age ≥ 70?		
Has the patient currently been admitted with a severe/terminal medical illness?		
Does the patient's immediate history note any history of Depression?		
Does the patient suffer from any significant visual impairment?		
Does the Patient currently have an indwelling catheter?		

3.3 Communication Barriers Present At Time Of Testing (Tick all that Apply)

Deafness		Dysphonia		Language Barrier	
Visual Impairment		Dysarthria			

Translator used during testing	Y	N

3.4 Patient Education

Literate (i.e Can patient read & write?)	Y	N	**Home Language**	Home Language
Has patient had any schooling?	Y	N		

Completed Grade?	0	1	2	3	4	5	6	7	8	9	10	11	12	College/University?	Y	N

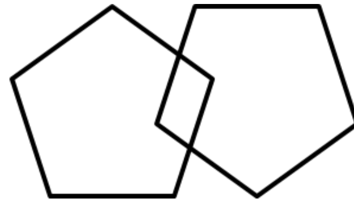
3.5 DSM IV Criteria for Delirium (complete at end with overall assessment)

Y	N	**Disturbance of consciousness** **(i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.**
Y	N	**A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia**
Y	N	**The disturbance developed over a short period of time (usually hours to days) and tends to fluctuate during the course of the day**
Y	N	**There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.**

3.6 Mini Mental State Examination (MMSE)

Instructions: Ask the questions in the order listed. Score 1 point for each correct response within each question or activity

Max Score	Q Score	Patients Score	Questions
5			"What is the Year? Season? Date? Day of the Week? Month?"
5			"Where are we now: Country? Province? Town/City? Hospital? Floor?
3			Examiner names three unrelated objects clearly and slowly (e.g. Ball, Flag, and Table). The patient is asked to repeat all three objects. Give one point for each. The Examiner repeats them until the patient learns all of them, if possible. Number of Trials : _______________
5			"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65) Alternative: "Spell WORLD Backwards." (D-L-R-O-W) One point for each correct answer.
3			"Earlier I told you the names of three things. Can you tell me what those were?" One point for each correct answer.
2			Show the patient two simple objects (e.g. Wristwatch, Pen/Pencil). Ask the patient to name them. Give one point for each correct answer.
1			"Repeat the phrase: 'No ifs, ands, or buts.'"
3			"Take this paper in your right hand, fold it in half, and put it on the floor" (Give patient a blank piece of paper)
1			"Please read this and do what it says." (Written instruction is "Close your Eyes.")
1			"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1			"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks patient to draw the symbol below. All 10 angles must be present and the two shapes must intersect



30	TOTAL

Cognitive Impairment suggested on MMSE?	None (≥25/30)		Mild (19-24/30)		Moderate (10-18/30)		Severe (≤9/30)	

Unable to complete MMSE	Y	N
If Yes, Reason:	Reason unable to complete	

3.7 Confusion Assessment Method (CAM)

Evaluation Test	Response (Please Circle)	
Acute onset and fluctuating course	**BOX 1**	
Is there evidence of an acute change in mental status from the Patient's baseline?	**NO**	**YES**
Did the (abnormal) behaviour fluctuate during the day, i.e. does it tend to come and go or increase and decrease in severity?	**NO**	**YES**
Inattention		
Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what is being said?	**NO**	**Yes**
Disorganised Thinking	**BOX 2**	
Was the patient's thinking disorganised or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?	**NO**	**YES**
Altered Level Of Consciousness		
Overall, how would you rate this patient's level of consciousness? **Alert (Normal)** **Vigilant (Hyper alert)** **Lethargic (drowsy, easily aroused)** **Stupor (Difficult to arouse)** **Coma (Unarousable)** **Do any checks appear in the box above?**	**NO**	**YES**

If <u>all the items in BOX 1</u> are checked <u>and</u> <u>at least one item in BOX 2</u> is check, then a diagnosis of delirium is suggested.

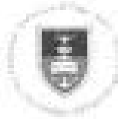
4. Overall Summary Of Reference testing

Delirium Suggested by DSM 4 Criteria?	Y	N
Delirium Suggested by MMSE Assessment?	Y	N
Delirium Suggested by CAM Assessment?	Y	N
Delirium Suggested by Overall Interview	Y	N

Please ensure that **This Form** is returned to Study Coordinator on day of completion

If RACY form is in folder – Please collection this as well an return to Study coordinator

Appendix 4: Ethics Approval



UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

15 May 2017

HREC REF: 311/2017

A/Prof J Peter
Department of Internal Medicine
J-floor
OMB

Dear A/Prof Peter

PROJECT TITLE: DELIRIUM AMONGST HIV-INFECTED GENERAL MEDICAL ADMISSIONS IN CAPE TOWN, SOUTH AFRICA (Mmed-candidate- Dr C Day)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 May 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student, Dr C Day will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 311/2017

Appendix 5: Lancet HIV Instructions to Authors

The Lancet HIV **is an exclusively online journal dedicated to publishing original research that advocates change in, or illuminates, HIV clinical practice. We will publish translational, epidemiological, clinical, operational, and implementation studies. All original research judged eligible for consideration by the journal's editors will be peer-reviewed within 72 h and, if accepted, published online within 8 weeks from submission. The journal will also publish relevant commentary and correspondence. Wherever possible, figures and good quality photographs (colour or black and white) should be used to supplement and to enhance the text. We also welcome videos. Further details on the different sections of *The Lancet HIV*, and how to submit to the journal, are provided below. If you require further clarification, the journal's editorial staff will be pleased to help (email TheLancetHIV@lancet.com).**

Manuscripts must be solely the work of the author(s) stated, must not have been previously published elsewhere, and must not be under consideration by another journal. *The Lancet* journals are signatories of the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, issued by the International Committee of Medical Journal Editors (ICMJE Recommendations) and to the Committee on Publication Ethics (COPE) code of conduct for editors. We follow COPE's guidelines.

Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals
http://www.icmje.org

COPE Code of Conduct
http://publicationethics.org/files/u2/New_Code.pdf

How to submit your paper

Manuscript submission

Manuscript submission to all *Lancet* journals is free. Manuscripts should be submitted online via the *The Lancet HIV's* online submission and peer review website (known as EES) at http://ees.elsevier.com/thelancethiv.

- Simply log on to EES and follow the on-screen instructions for all submissions.
- If you have not used EES before, you will need to register first. In EES, the corresponding author is the person who enters the manuscript details and uploads the submission files.
- Inclusion of illustrations (photographs, graphs, diagrams, etc) is a prerequisite for publication. Submission of original and editable artwork files is encouraged. Digital photography files should have a resolution of at least 300 dpi and be at least 107 mm wide. . Before and after images should be taken with the same intensity, direction, and colour of light.
- In almost all cases, if you have a finished manuscript, you should submit it, rather than contacting *The Lancet HIV* to enquire whether an unseen manuscript is likely to be accepted. Unless you have been asked by the Editor to submit by email, you should use the online system for all types of submission, including Correspondence.
- If you have any technical problems or questions, please contact our dedicated customer support:

    For the Americas: +1 888 8347287 (09:00 to 17:00 central standard time)
    For Asia and Pacific: +81 3 55615032 (09:30 to 17:30 Japan standard time)
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1. Covering letter
2. Manuscript including tables and panels
3. Figures
4. Author statement form (see next section)
5. Declaration of interests and source of funding statements (see next section)
6. In-press papers—one copy of each with acceptance letters
7. Protocols and CONSORT details for randomised controlled trials (see Articles)
8. We encourage disclosure of correspondence from other journals and reviewers, if previously submitted, and we might contact relevant editors of such journals
9. Research in context panel, for all primary research Articles

- Use the covering letter to explain why your paper should be published in *The Lancet HIV* rather than elsewhere

Statements, permissions, and signatures

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- Designated authors should meet all four criteria for authorship in the ICMJE Recommendations
- All authors, and all contributors (including medical writers and editors), should specify their individual contributions at the end of the text.
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ICMJE Recommendations
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Author statement form
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Forms and signatures

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These statements can be scanned and submitted electronically with your submission. Please note that *The Lancet* journals will accept hand-signed and electronic (typewritten) signatures.

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- At the end of the text, under a subheading "Declaration of interests", all authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of financial conflicts include employment, consultancies, stock ownership, honoraria, paid expert testimony, patents or patent applications, and travel grants, all within 3 years of beginning the work submitted. If there are no conflicts of interest, authors should state that none exist.
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ICMJE COI form
http://www.thelancet.com/for-authors/forms#icmje-coi
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Patient Consent form
http://www.thelancet.com/pb/assets/raw/Lancet/authors/lancet-consent-form.pdf

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- At the end of the Methods section, under a subheading "Role of the funding source", authors must describe the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.
- If there is no Methods section, the role of the funding source should be stated as an acknowledgment. If the funding source had no such involvement, the authors should state this.
- The corresponding author should confirm that he or she had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Please ensure that anything you submit to *The Lancet HIV* follows the guidelines provided for each article type. For instruction on how to format the text of your paper, including tables, figures, panels, and references, please see our **Formatting guidelines.**

Red section (Articles)

Articles

- *The Lancet HIV* prioritises reports of original research that are likely to change clinical practice or thinking
- We invite submission of all clinical trials, whether phase 1, 2, 3, or 4. For phase 1 trials, we consider those of a novel substance for a novel indication, if there is a strong or unexpected beneficial or adverse response, or a novel mechanism of action.
- We require the registration of all interventional trials, whether early or late phase, in a primary register that participates in WHO's International Clinical Trial Registry Platform (see *Lancet* 2007; **369:** 1909–11) or in ClinicalTrials.gov, in accord with ICMJE recommendations. We also encourage full public disclosure of the minimum 20-item trial registration dataset at the time of registration and before recruitment of the first participant (see *Lancet* 2006; **367:** 1631–35). The registry must be independent of for-profit interest.
- Reports of trials must conform to CONSORT 2010 guidelines and should be submitted with their protocols.
- All reports of randomised trials should include sections entitled Randomisation and masking and Outcomes, within the Methods section. Please refer to *The Lancet*'s formatting guidelines for randomised trials.
- Cluster-randomised trials must be reported according to CONSORT extended guidelines.
- Randomised trials that report harms must be described according to extended CONSORT guidelines.
- Studies of diagnostic accuracy must be reported according to STARD guidelines.
- Observational studies (cohort, case-control, or cross-sectional designs) must be reported according to the STROBE statement, and should be submitted with their protocols.
- We encourage the registration of all observational studies on a WHO-compliant registry (see *Lancet* 2010; **375:** 348).
- Genetic association studies must be reported according to STREGA guidelines.
- Systematic reviews and meta-analyses must be reported according to PRISMA guidelines. Please refer to *The Lancet*'s formatting guidelines for systematic reviews and meta-analyses.
- Reports of studies of global health estimates should be reported according to the GATHER statement (see *Lancet* 2016; published online June 28. http://dx.doi.org/10.1016/S0140-6736(16)30388-9)
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All Articles should, as relevant

- Be up to 3500 words (4500 for randomised controlled trials) with 30 references (the word count is for the manuscript text only).
- Include an abstract (semistructured summary), with five paragraphs (Background, Methods, Findings, Interpretation, and Funding), not exceeding 250 words. Our electronic submission system will ask you to copy and paste this section at the "Submit Abstract" stage.
- For randomised trials, the abstract should adhere to CONSORT extensions: abstracts (see *Lancet* 2008; **371:** 281–83).
- When reporting Kaplan-Meier survival data, at each timepoint, authors must include numbers at risk, and are encouraged to include the number of censored patients.
- For intervention studies, the abstract should include the primary outcome expressed as the difference between groups with a confidence interval on that difference (absolute differences are more useful than relative ones). Secondary outcomes can be included as long as they are clearly marked as secondary and all such outcomes are reported.
- Use the SI system of units and the recommended international non-proprietary name (rINN) for drug names. Ensure that the dose, route, and frequency of administration of any drug you mention are correct.
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- Include any necessary additional data as part of your EES submission.
- All accepted Articles should include a link to the full study protocol published on the authors' institutional website (see *Lancet* 2009; **373:** 992 and *Lancet* 2010; **375:** 348).
- We encourage researchers to enrol women and ethnic groups into clinical trials of all phases, and to plan to analyse data by sex and by race
- For all study types, we encourage correct use of the terms sex (when reporting biological factors) and gender (when reporting identity, psychosocial, or cultural factors). Where possible, report the sex and/or gender of study participants, and describe the methods used to determine sex and gender. Separate reporting of data by demographic variables, such as age and sex, facilitates pooling of data for subgroups across studies and should be routine, unless inappropriate. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data.

Putting research into context

- All research papers (including systematic reviews/meta-analyses) submitted to any journal in *The Lancet* family must include a panel

WHO's International Clinical Trial Registry Platform
http://www.who.int/ictrp/network/trds/en/index.html

Clinical trials
http://clinicaltrials.gov

ICMJE recommendations
http://icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

CONSORT 2010 guidelines
http://www.consort-statement.org/consort-2010

CONSORT extended guidelines
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STARD guidelines
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http://www.strobe-statement.org/

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http://www.prisma-statement.org/

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GATHER statement
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30388-9/fulltext

To find reporting guidelines, see
http://www.equator-network.org

MENDELEY data
https://data.mendeley.com

Human Gene Organisation
http://www.genenames.org/

MIAME guidelines
http://fged.org/projects/miame/

Array and GEO
http://www.ebi.ac.uk/microarray-as/ae/
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putting their research into context with previous work in the format outlined below (see *Lancet* 2014; **384**: 2176–77, for the original rationale). This panel should not contain references. Editors will use this information at the first assessment stage and peer reviewers will be specifically asked to check the content and accuracy.

- The Discussion section should contain a full description and discussion of the context. Authors are also invited to either report their own, up-to-date systematic review or cite a recent systematic review of other trials, putting their trial into context of the review.

For The Lancet journals' policy on corrections of errors see **www.thelancet.com/for-authors/forms#correction**

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Formatting guidelines for randomised trials
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Research in context

Evidence before this study

This section should include a description of all the evidence that the authors considered before undertaking this study. Authors should briefly state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including the exact start and end dates of the search), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate.

Added value of this study

Authors should describe here how their findings add value to the existing evidence.

Implications of all the available evidence

Authors should state the implications for practice or policy and future research of their study combined with existing evidence.

Research in context panels should not contain references; key studies mentioned here should be referenced in the main text.

Blue section (Comment, Correspondence)

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- Editorials are the voice of *The Lancet HIV*, and are written in-house by the journal's editorial-writing team and signed "*The Lancet HIV*".

Comment

- This section contains Comments that accompany papers published in *The Lancet HIV* or on issues of wide-reaching concern in HIV. Most are commissioned, but unsolicited Comments (no more than 750 words, 10 references, and one figure, panel, or small table) are also welcome. Comments may be peer reviewed.
- The place to respond to something we have published is in our **Correspondence** section.
- See **Conflicts of Interest** guidelines for comments.

Correspondence

- Letters can be written in response to previous content published in *The Lancet HIV*.
- Letters for publication must reach us within 4 weeks of publication of the original item and should be no longer than 400 words.
- Letters of general interest, unlinked to items published in the journal, can be up to 400 words long.
- Correspondence is not usually peer reviewed, but we might invite replies from the authors of the original publication, or pass on letters to these authors.
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- Any substantial error in any article published in *The Lancet HIV* should be corrected as soon as possible. Blame is not apportioned; the important thing is to set the record straight.
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- Type a single space at the end of each sentence
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- Cite references in the text sequentially in the Vancouver numbering style, as a superscripted number after any punctuation mark. For example "...as reported by Saito and colleagues.[15]"
- Two references are cited separated by a comma, with no space. Three or more consecutive references are given as a range with an en rule. To create an en rule on a PC hold down CTRL key and minus sign on the number pad, on a Mac ALT hyphen.

- References in tables, figures, and panels should be in numerical order according to where the item is cited in the text.
- Here is an example for a journal reference (note the use of tab, bold, italic, and the en rule):
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- Give any subpart to the title of the article.
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  surname space initials comma
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Drug names

- Recommended international non-proprietary name (rINN) is required
- We encourage use of neuroscience-based nomenclature for psychotropic drugs

References

- Vancouver style as above.
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Audio
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Drug names
For more on neuroscience-based nomenclature see http://www.thelancet.com/pdfs/journals/lanpsy/PIIS2215-0366(17)30098-6.pdf

containing a reference number, which should be used in all future communications.

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