Management of post-infectious hydrocephalus in people living with HIV

A prospective observational study

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Table of contents:

1. Declaration

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2. List of Tables

3. List of Figures

4. Abbreviations

HIV	human immunodeficiency virus
AIDS	acquired immunodeficiency syndrome
TB	tuberculosis
TBM	tuberculous meningitis
CCM	cryptococcal meningitis
PIH	post infectious hydrocephalus
CSF	cerebrospinal fluid
VPS	ventriculoperitoneal shunt
EVD	external ventricular drain
LP	lumbar puncture
F	favourable
UF	unfavourable
GCS	Glasgow Coma Scale
mRS	modified Rankin Scale
SAMJ	South African Medical Journal
UNAIDS	Joint United Nations Programme on HIV/AIDS
SAHCS	South African HIV Clinician Society

5. Publication ready manuscript

5.1. Abstract

Background

Post-infectious hydrocephalus (PIH) in people living with HIV (PLHIV) is a common complication presenting to neurosurgeons in South Africa, but there is limited evidence to guide management of these patients.

Objectives

The study aimed to prospectively document the in-hospital management and 12 month neurological and survival outcomes of PIH in people living with HIV (PLHIV).

Methods

The study included a consecutive series of 23 people living with HIV (PLHIV) presenting to a tertiary hospital in 2018 with a diagnosis of post infectious hydrocephalus who were followed up for a 12-month period. Baseline demographics, HIV data, and Glasgow Coma Score, aetiology of post infectious hydrocephalus and treatment modality were documented. Survival outcomes and neurological function (modified Rankin Scale) were assessed. The cohort was divided into non-randomised treatment groups, surgical (ventriculoperitoneal shunts/ external ventricular drain) and medical (lumbar spinal taps) based on institutional practice.

Results

PIH aetiologies were noted as tuberculous in 78.3% (n=18) and cryptococcal in 21.7% (n=5). Overall survival at discharge was 69,9% (n=16) and 47.8% (n=11) at 12 months follow up. Functional outcomes expressed as mRS, resembled the survival data, showing favourable outcomes at 12 months within the survival group. Linear regression analysis showed that the cohort had an unchanged mRS during the 12-month period (p=0.008)

Conclusion

The limited data from this study suggest that a proactive therapeutic approach to PIH should be offered to virologically suppressed individuals. A tiered treatment algorithm is proposed to guide the treatment of these patients. Further studies using this treatment algorithm could provide a more accurate representation of outcomes in this population.

What the study adds

People living with HIV presenting with PIH secondary to TBM, who are on ART should be considered for ventriculoperitoneal shunts. This study proposes the use of a treatment algorithm to triage patients into an appropriate treatment pathways based on ART treatment status. The treatment algorithm should be considered for other aetiologies of PIH.

5.2. Manuscript

5.2.1. Introduction

The updated Joint United Nations Programme on HIV/ AIDS (UNAIDS) reports 79% of HIV infected adults in the Eastern and Southern African region to be on antiretroviral therapy, with 74% virologically supressed.[1] South Africa has seen a 50% reduction in new HIV infection since 2010 and a 73% reduction in AIDS-related deaths.[1] Current HIV incidence-prevalence ratio is reported as 2.8 in South Africa, with 67% virologically supressed.[1] Accurate reporting of the incidence with regards to TB and CCM co-infection is lacking, but TB co-infection has been estimated at a two-third reduction in the last decade.[1] Despite the fall in overall HIV complications, neurological complications in HIV infected patients continue to be a clinical challenge.[2,3]

Post infectious hydrocephalus (PIH) is a common neurological complication in the HIV-infected population. The management of PIH is challenging with multiple approaches and treatment modalities.[4,5] This is further complicated by HIV disease severity and tuberculous and cryptococcal co-infections.[1] Due to the sparsity of clinical evidence and long term survival studies, there are no standardized guidelines for the management of PIH in PLHIV.

The Southern African HIV Clinician Society (SAHCS) has published recommendations regarding the treatment of tuberculous and cryptococcal meningitis in the HIV population.[6–10] This includes early diagnosis and initiation of antimicrobial therapy, controlling raised intracranial pressure with steroids, diuretics and in cases where communicating hydrocephalus is present, therapeutic lumbar punctures in a tiered approach. However, within the neurosurgical context, there is no consensus regarding surgical intervention for PIH.[5]

The most recent studies done for tuberculous meningitis (TBM) and cryptococcal meningitis (CCM) [6,7] in PLHIV documented good survival outcomes in a select group of patients, those with a high CD4 count, low viral load and on antiretroviral treatment, presenting with a GCS >8, early disease detection, rapid initiation of appropriate antimicrobial therapy and treatment of raised intracranial pressures. However, this presents a challenge in determining treatment for patients with PIH excluded from these studies, and developing an effective treatment algorithm that could be used across multiple centres.

In view of the advances in care for this population through earlier initiation of antiretroviral therapy (ART) with higher overall survival, evaluating the outcome of current clinical practice in managing PIH may help establish a guideline for management of this condition.

5.2.2. Methods

Study design

A prospective observational study was conducted at Groote Schuur Hospital (GSH), a tertiary hospital with both Neurosurgery and Infectious Disease services. This study included a consecutive series of 23 HIV-infected patients presenting with PIH, confirmed on a brain computed tomography (CT) and managed as per GSH standard practice of care (medical or surgical) and followed up for 12 months post initial presentation.

PIH was defined as a CT Brain report of hydrocephalus; and a ventricular or lumbar CSF results suggestive of meningitis in people living with HIV. Patients who had meningitis with raised intracranial pressure, but were not treated for hydrocephalus were excluded from the study; as were those who were previously treated for PIH and re-presented with complications due to ventriculoperitoneal shunt (VPS) dysfunction or HIV disease progression. GSH standard of care includes early initiation of appropriate antimicrobial therapy and treatment of Raised intracranial pressures (i.e. steroids and diuretics in cases of TBM; therapeutic lumbar taps in CCM)

The primary objective of the study was survival at 12 months' post intervention. Secondary objectives were outcomes in neurological function, expressed using the modified Rankin Scale (mRS).

The following variables were collected:

- Baseline demographic data including age, sex (expressed as male or female) and HIV data (timing of diagnosis and exposure to ART)
- Clinical parameters included presenting symptoms, Glasgow Coma Scale (GCS), and neurological deficits
- Laboratory data included CD4 count, viral load, and CSF analysis. Data was categorised for statistical analysis:
    - CD4 was categorised into >200 cells/ul; 200-100 cells/ul and <100 cells/ul
    - viral load was categorised into supressed (<50 copies/ml) and unsuppressed (>50 copies/ml)
    - TBM was defined according to the Marais criteria [11,12]and CCM confirmed by a positive CSF cryptococcal latex antigen test (CLAT) or a positive cryptococcal culture on CSF.
- Imaging data was from computed tomography (CT) findings of hydrocephalus.
- Lumbar punctures with opening pressures were documented. Pressures of >20mmHg were used as surrogate markers for hydrocephalus.

- Admission parameters included in-patient days, modality of CSF diversion (medical vs surgical) and outcomes at discharge (in-hospital mortality, discharge GCS)

- Follow up parameters included survival and functional neurological outcomes (mRS) at one, six and twelve months.

- Data capture systems used included questionnaires, Clinicom e-service and the JAC Pharmacy system (Western Cape Department of Health electronic systems for centralised admissions and dispensing of medicines)

- Patients were further divided into a medical and surgical treatment groups, based on institutional practice. GSH institutional practice refers patients who are virologically suppressed with a good premorbid baseline, who present with a GCS > 8 and a proven rapid deterioration in level of consciousness for surgical treatment. All others are treated medically.

- As per GSH standard of care, the medical treatment was defined as daily lumbar punctures according to protocol[6,7] in additional to antimicrobial therapy, diuretics and steroids in cases of TBM; and surgical treatment was defined as an external ventricular drain or ventriculoperitoneal shunt.

Statistical analysis

The software R Studio v2022.07 was used to perform statistical analysis. Statistical analyses were conducted for baseline demographic data, admission data, as well as short and long-term outcomes. Student's t-tests, and χ^2 were utilized for parametric and non-parametric continuous and categorical variables, respectively. Linear regression models were used for change in mRS at 6 and 12-months post intervention. P=0.05 was considered significant.

5.2.3. Results

Demographic data

A total of 23 patients were seen from April 2018 to March 2019 and each patient was followed for up to 12 months. Of all the patients referred during the recruitment period, none were excluded from the study based on the exclusion criteria. The cohort showed similar patient demographics within the two treatment groups (Table 1), with an overall median age of 39 years (IQR 32 - 43.5) and an almost even distribution between males and females (52.2% and 47.8 % respectively). Only 21.7% were newly diagnosed as HIV infected, with 78.2% of the total cohort previously diagnosed, either currently on ART (56.5%) or previously exposed to ART (21.7%).

Fifteen of the patients underwent medical treatment (serial lumbar punctures and diuretics) and are referred to as the medical group in this study. The surgical group (n=8) were treated either with a ventriculoperitoneal shunt (VPS) or external ventricular drain (EVD).

Admission Data

The main presenting complaints were noted as confusion or altered level of consciousness in 86.9% of the total cohort. The GCS was further categorized into mild (13-15), moderate (12-8) and severe (<8). Overall, the cohort presented predominantly in the mild category (65.2%), with no significant difference between the two treatment groups (p=0.74). The majority of the cohort, as demonstrated in Table 1, had a CD4 count <100 (65%), with the rest of the cohort evenly distributed between the >200 (17.4%) and 100-200 categories (17.4%) with no difference between the treatment groups (p=0.744),

Virologically suppressed patients accounted for 26 % of the total cohort with higher numbers noted within the surgical group (37.5% vs 20%) although this was not significant (p=0.622); 39.1% of the total cohort were virologically unsuppressed, and no virological data was available in 34.8 %.

All patients had a CTB reporting hydrocephalus. A total of 15 patients underwent lumbar puncture and had admission CSF parameters recorded. Of the 15 patients, opening pressures >20mmHg were noted in 5, 3 patients had opening pressures below 20mmHg and in 7 patients opening pressures were not documented. An air encephalogram was done in 5 patients to establish if hydrocephalus was communicating or non-communicating. The subgroup treated surgically (n=8), had lumbar punctures deferred at presentation, and no ventricular opening pressures were performed.

CCM was diagnosed in 21.7% and the rest of the cohort had TBM according to the Marais criteria, either definite (17.3%), probable (30.4%) and possible (30.4%).[11] Data was collected for commencement of antimicrobial therapy on admission. Early commencement of antimicrobial therapy was noted at 91.3% of the cohort, based on clinical suspicion of meningitis.

Short term outcome

Patients were admitted for a mean of 15.8 in-patient days (range 3-49). Overall in-patient survival was noted as 69.9%, with no significant difference between the medical (66.7%) and surgical (75%) subgroups (p= 0.469) as shown in Table 2. Of the survivors, 34.8% of patients were discharged with a GCS of 15/15 and 26.1% had a discharge GCS of 14/15. There were no significant differences in discharge GCS between the two treatment groups (p=0.627) Patient disposition was noted as discharged home (12.5%), transferred to secondary level hospital (33.3%) or to a long-term care facility (37.5%).

Within the surgical treatment group, 4 patients (50%) underwent a ventriculoperitoneal shunt insertion as primary mode of CSF diversion while the other 4 patients underwent a trial of external ventricular drain (EVD), of whom 2 died and 2 improved and were discharged without permanent CSF diversion (VPS). One patient within the VPS treatment group required VPS revision within 3 months.

Long term outcome

Outcomes are reported in Table 2. Overall survival was 60.9% at one month with the cohort showing a progressive decline in survival at the six months (52.2%) and twelve months (47.8%) time points. This progressive decline was reported within the medically treated cohort while the surgically treated cohort remained unchanged from 6 months to 12 months (50% alive).

Neurological outcomes were categorized using mRS into favourable (mRS 0- 3) and unfavourable (mRS 4-6). Functional neurological outcome mirrored survival outcomes. A favourable mRS was noted in 43.5% of the total cohort at 1 month, 47.8% at six months and 39.1% at 12 months. The medically treated group showed a progressive decline at each time point, while the surgical group remained unchanged (50%) at all time intervals. Overall, there was no change in mRS score from one month to twelve months (p=0.008).

5.2.4. Discussion

This study set out to determine outcome following treatment of PIH in HIV infected patients. This small cohort demonstrated an overall survival of 70% at discharge, with a further decline over the 12-month period. Of note, the treatment group that underwent permanent CSF diversion via VPS, had an unchanged survival and functional neurological outcome throughout the study period. One of the challenging aspects of managing this condition is when patients present acutely with clinical deterioration from hydrocephalus. The burden of managing these patients often falls on medical teams in the district level as the first point of contact, with delayed referral to tertiary centres or incorrect treatment. Furthermore, opening pressures may not be routinely performed with the index lumbar puncture, leading to inappropriate management of the RICP leading to a delayed referral for more definitive management. A clinically relevant treatment guideline may improve overall management and survival outcomes in this population.

Bicanic and colleagues demonstrated that repeated lumbar punctures during treatment of CCM not only controlled RICP but also reduced fungal burden, in turn improving overall outcomes in this cohort.[13,14] The use of lumbar punctures to control PIH following CCM was echoed by Rolfes and colleagues who also reported 69% relative improvement in survival with repeated lumbar punctures.[15] Both studies cited lack of protocolised guidelines including non-uniformity in performing the procedure, non-recording of opening pressures due to equipment shortages (manometers) or lack of knowledge as potential factors influencing their findings. This is in keeping with findings in this study with missing data (opening pressures) noted in 65.2% (n=15) of the total cohort. This data suggests that PIH in the acute setting is potentially under-recognised and not optimally treated.

On the surgical front, previously published data focus on surgical treatment of PIH (VPS insertion) in the context of TBM,[16–17] as is the case with the present study. This has been attributed to the endemic nature of tuberculosis and HIV co-infection in the region. In South Africa, TBM has been reported with mortality rates approaching 50%[19] despite a reported 65% overall decline in AIDS related mortality.[1] PIH secondary to CCM has far less data reported for VPS insertion. This has been attributed to more readily accessible medical

recommendations in the management of PIH secondary to CCM[6, 9] Additionally, lower intracranial pressures are reported in CCM as compared to TBM on measuring lumbar CSF opening pressures. CCM pressures seldom exceed 35cmH_2O (25mmHg) as compared to TBM where pressures often exceed 50cmH_2O (36mmHg).[13–15] It is for this reason, and a satisfactory response to non-surgical treatment[13] that PIH secondary to CCM is not routinely considered for VPS, and patients are typically managed with serial lumbar punctures.[13,14]

The most frequently cited study with regards to surgical treatment of PIH was done by Nadvi and colleagues in the pre-ART era, which concluded that patients with PIH secondary to TBM should undergo a trial of EVD and only those who improve should receive a VPS.[16] These findings were echoed by Sharma and colleagues who included a subset of patients who could undergo a VPS as first line provided they had a good Palur grade.[17] In contrast to previous reports, findings in the current study noted that patients who underwent trial of CSF diversion via EVD, either improved and were discharged without a VPS (n=2) or they succumbed to the disease process (n=2). These results suggest that may be a subset of patients who deteriorate acutely because of the raised intracranial pressures, and would have a lower Palur grading on presentation, but could improve clinically with a VPS as a first line of treatment. Kankane et al[20] reported similar findings in their study's 50 patient cohort which demonstrated good outcomes at 3 months in patients with Palur grade III and IV.[20] This decision making could be troublesome for junior doctors in district hospitals who are not experienced with treating these patients, adding to the need for standard guidelines for evaluation and referral pathways to institutions where more experienced colleagues could make this distinction.

There is minimal data published regarding long term survival and neurological outcomes following treatment of PIH in HIV-infected patients, with most studies citing small samples sizes, very narrow patient selection and poor follow ups as factors influencing accurate reporting.[18] The multitude of therapeutic options offered in this population was also noted to be a factor when attempting to accurately describe outcomes, with different studies showing very wide range of outcomes depending on the treatment modality. The challenge of reporting a wide range of survival data from informed estimates and lack of long-term follow-up data, can perpetuate nihilistic clinician attitudes to justify non-intervention in this patient cohort despite documented improved global HIV data.

Significantly, Harrichandparsad and colleagues[18] reported one month survival outcomes greater than 70% in patients who were on ART despite having low absolute CD4 count values.[18] Their study identified ART as an independent factor for survival, where previously the severity of hydrocephalus was considered to be the determining factor. Likewise, in the present study patients who were virologically suppressed and on ART, who received a VPS as a primary mode of CSF diversion had better outcomes at 12 months. This contrasted to previous studies who reported treatment methods as a predictor of outcome.[16,17] The current study did not seek to eliminate the EVD trials but rather streamline it to those patients whose clinical picture is in question because of their virological data rather than severity of hydrocephalus. This observation perhaps supports the hypothesis that outcomes were linked to choosing the appropriate treatment pathway, based on the patient's initial clinical data.

Despite the small sample size, the current study extends the survival timeline reported by Harrischandparsad with all patients who received a VPS were alive at one month, surviving to 12 months. Long term neurological outcomes were also favourable in the patients who

were virologically suppressed and or on ART. Both the medical and surgical treatment subgroups, reported favourable outcomes in functional neurological outcome (mRS) despite the majority of the cohort having a CD4 count below 100 cells/ul. In this study, ART and baseline viral load (<50copies/ml) were suggestive to be good predictors of outcome, irrespective of the Palur grade at presentation. Similar to the surgically treated subgroup, virological data was also noted to be an independent predictor of outcome in the group treated with serial LP's.

As previously noted, the lack of opening pressures reported in this study played a role by limiting accurate analysis of the data. This proved a limitation to potentially identify variables that could aid in determining patients who would benefit from a surgical approach as first line of treatment versus those that could undergo a trial of non-surgical treatment and probability for resolution without the need for VPS. Standard guidelines could also identify variables that could predict failure of medical treatments to aid in the early referral pathways and better follow-up of patient outcomes.

The lack of routine LP opening pressures, was mostly attributed to busy emergency rooms, equipment shortages, lack of knowledge and or documentation of opening pressures by the initial physicians performing the procedure.[14] This resulted in a significant loss of data to quantify the pressure difference between the two aetiologies. In the study, it was noted that within the two treatment groups, CSF opening pressures were performed and documented at higher frequency within the medical subgroup than the surgically treated subgroup, emphasising the widely available recommendations.[6,7,9] The recording of CSF opening pressure measurements in the surgical subgroup is not routine practice in most institutions. This is mostly attributed to the urgency and clinical picture with which the patients presented, with acutely raised intracranial pressure requiring emergent diversion. In the medically treated subgroup, 33% of the total cohort (n=5) had opening pressures above 20mmHg and showed similar results as previous studies with higher opening pressures in TBM than CCM.[13-15,19] However, due to lack of large numbers or heterogeneity of the data, this result was not statistically significant.

Further limitations noted in this study were those of a small sample size in providing statistically significant results. Additionally, within the surgical subgroup, the study acknowledges the homogeneity of the cohort, as all patients who received a VPS had TBM as an etiological cause. Thus, true observations cannot be concluded regarding outcomes of patients undergoing VPS with a CCM aetiology. For such a recommendation to be made, a study with a larger sample size would have to be conducted with both TBM and CCM aetiologies undergoing VPS. Despite having a small sample size, this study provides valuable data with regards to optimally treating PIH patients, and has documented prospectively their outcomes following treatment. This study also provides an accurate representation of their functional outcomes long term, which is lacking in the literature within this patient population. The results from this study may be helpful in developing a novel approach to the treatment of PIH in HIV infected patients.

5.2.5. Conclusions

PIH in HIV infected patients has severe complications when there is a delay to diagnosis and treatment with initiation of appropriate antimicrobials therapy and emergent CSF diversion. There are multiple modalities instituted in treatment of PIH in the acute setting with few studies reporting good survival outcomes following therapy. However, there is no overall consensus amongst institutions regarding standardisation of treatment. Randomised and long term follow up studies are still lacking, especially those supporting a surgical approach (VPS). The results of this study demonstrated that patients treated with VPS may not only have good survival outcomes at twelve months, but also favourable functional neurological outcome (mRS). In both the medical and surgical subgroups, patients who were virologically suppressed and or on antiretroviral treatment had higher survival rates. This data suggests that a more active and involved therapeutic approach should be taken with this subgroup of patients.

Based on these findings, the authors propose the use of a treatment algorithm (Figure1) to guide a systemic approach to CSF diversion in this population. This may optimise the use of resources already in place thereby improving overall outcomes. A treatment algorithm will quickly identify patients who would benefit from permanent CSF diversion from the outset, and differentiate them from patients unlikely to benefit from such intervention. This triage system will effectively direct resources to more eligible candidates whilst still ensuring best medical care for those with advanced disease. In addition, data collected from the utilisation of this systematic approach, can be used to guide further research into PIH from CCM and other causative agents, adding to future randomised studies, where a more evidence-based treatment algorithm can be formulated.

5.2.6. Acknowledgements

The authors would like to thank the staff at Groote Schuur Hospital for their assistance with identifying potential study participants.

Authors' contributions

R.M.L was the primary author and was responsible for the study design, data collection, data analysis, manuscript write-up, revision and approval of the final manuscript. A.G.F and S.K.D assisted with the study design, interpretation of results, revision and approval of the final manuscript.

Ethical considerations

- This study was reviewed and approved by the Human Research Ethics Committee (HREC), the Surgical Department of Research Committee (DRC) both at UCT. Study approval number: HREC REF: 069/2018
- Institutional approval was provided by the Groote Schuur Hospital CEO, Dr B. Patel.
- Consent to participate in the study was obtained voluntarily from individuals following informed counselling with the primary investigator, and signed for on

standard research consent forms. Consent was obtained both in a written and oral manner. In cases where the participants could not provide consent due to their clinical condition (a reduced GCS) next of kin consent was obtained by the primary investigator.

- Data was obtained using hospital records. Patient data was stored electronically in an access restricted files. Patient identifiers and any data pertaining to the participants in a personal nature was removed. Access to the data was limited to the primary investigator, with limited non-identifiable data accessed by the statistician for analysis. Original data collection sheets and consent (in paper format) were transcribed electronically, and access limited to the primary investigator.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Funding information

This research was self-funded and did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Data availability statement

Data pertaining to this study are available from the corresponding author, R.M.L, upon request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the institution or funder.

5.2.7. References

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5.2.8. Tables

Table 1 : Patient demographics and admission data

	Medical (n=15)	Surgical (n=8)	Total (n=23)	p-value
Age (Years)				**0.658**
Mean (SD)	38.3 (7.58)	40.4 (11.4)	39.0 (8.88)	
Median (IQR)	39.0 (32.5-41.5)	38.5 (32.5-45.3)	39.0 (32.0-43.5)	
Range	27.0-52.0	28.0-63.0	27.0-63.0	
Gender				**0.400**
Male	60% (n=9)	37.5% (n=3)	52.2% (n=12)	
Female	40% (n=6)	62.5% (n=5)	47.8% (n=11)	
ART				**0.177**
Naïve	33.3% (n=5)	0% (n=0)	21.7% (n=5)	
On treatment	46.7% (n=7)	75% (n=6)	56.5% (n=13)	
Previously exposed	20% (n=3)	25% (n=2)	21.7% (n=5)	
GCS admission severity				**0.688**
Mild (13-15)	66.7% (n=10)	62.5% (n=5)	65.2% (n=15)	
Moderate (12-8)	26.7% (n=4)	37.5% (n=3)	30.4% (n=7)	
Severe (<8)	6.7% (n=1)	0% (n=0)	4.3% (n=1)	

CD 4 count				**0.744**
Mild (>200)	13.3% (n=2)	25% (n=2)	17.4% (n=4)	
Moderate (100-200)	20% (n=3)	12.5% (n=1)	17.4% (n=4)	
Severe (<100)	66.7% (n=10)	62.5% (n=5)	65.2% (n=15)	
Viral load				**0.622**
Suppressed (<50 copies/ml)	20% (n=3)	37.5% (n=3)	26.1% (n=6)	
Unsuppressed (>50 copies/ml)	*40% (n=6)*	*37.5% (n=3)*	*39.1% (n=9)*	
Missing data	40% (n=6)	25% (n=2)	34.8% (n=8)	
LP opening pressures				**0.375**
<20cmH20	13.3% (n=2)	12.55 (n=1)	13% (n=3)	
>/= 20cmH20	33.3% (n=5)	0% (n=0)	21.7% (n=5)	
Not recorded	53.3% (n=8)	87.5% (n=7)	65.2% (n=15)	
Confirmatory test (air encephalogram)				**0.212%**
Negative	6.7% (n=1)	25% (n=2)	13% (n=3)	
Positive	13.3% (n=2)	0% (n=0)	8.7% (n=2)	

Type of meningitis				**0.2255**
CCM	26.7% (n=4)	12.5% (n=1)	21.7% (n=5)	
Definite TBM	26.6% (n=4)	0% (n=0)	17.3% (n=4)	
Probable TBM	26.7% (n=4)	37.5% (n=3)	30.4% (n=7)	
Possible TBM	20% (n=3)	50% (n=4)	30.4% (n=7)	

Table 2: Long term outcomes: Survival data and functional outcome data (mRS)

	Medical (n=15)	***Surgical (n=8)***	***Total (n=23)***	***p-value***
	Survival			
Discharge				**0.469**
Alive	66.7% (n=10)	75% (n=6)	69.6% (n=16)	
Died	33.3% (n=5)	25% (n=2)	30.4% (n=7)	
One month				**0.400**
Alive	53.3% (n=8)	75% (n=6)	60.9% (n=13)	
Died *	46.7% (n=7)	25% (n=2)	39.1% (n=9)	
Six months				**0.453**
Alive	53.3% (n=8)	50% (n=4)	52.2% (n=12)	
Died *	46.7% (n=7)	50% (n=4)	47.8% (n=11)	

Twelve months				**1.00**
Alive	46.7% (n=7)	50% (n=4)	47.8% (n=11)	
*Died **	53.3% (n=8)	50% (n=4)	52.2% (n=12)	
Modified Rankin Score				
One month				**0.685**
Favourable	40% (n=6)	50% (n=4)	43.5% (n=10)	
Unfavourable	60% (n=9)	50% (n=4)	56.5% (n=13)	
Six months				**1.00**
Favourable	46.7% (n=7)	50% (n=4)	47.8% (n=11)	
Unfavourable	53.3% (n=8)	50% (n=4)	52.2% (n=12)	
Twelve months				**0.657**
Favourable	33.3% (n=5)	50% (n=4)	39.1% (n=9)	
Unfavourable	66.7% (n=10)	50% (n=4)	60.9% (n=14)	
Change in mRS: one to twelve months.				***0.008***
Deterioration	13.3% (n=2)	12.5% (n=1)	13% (n=3)	
Improvement	13.3% (n=2)	12.5% (n=1)	13% (n=3)	
Unchanged	73.3% (n=11)	75% (n=6)	73.9% (n=17)	

***refers to cumulative deaths of the total cohort at subsequent time intervals.**

5.2.9. Figures

Figure 1: Proposed treatment algorithm

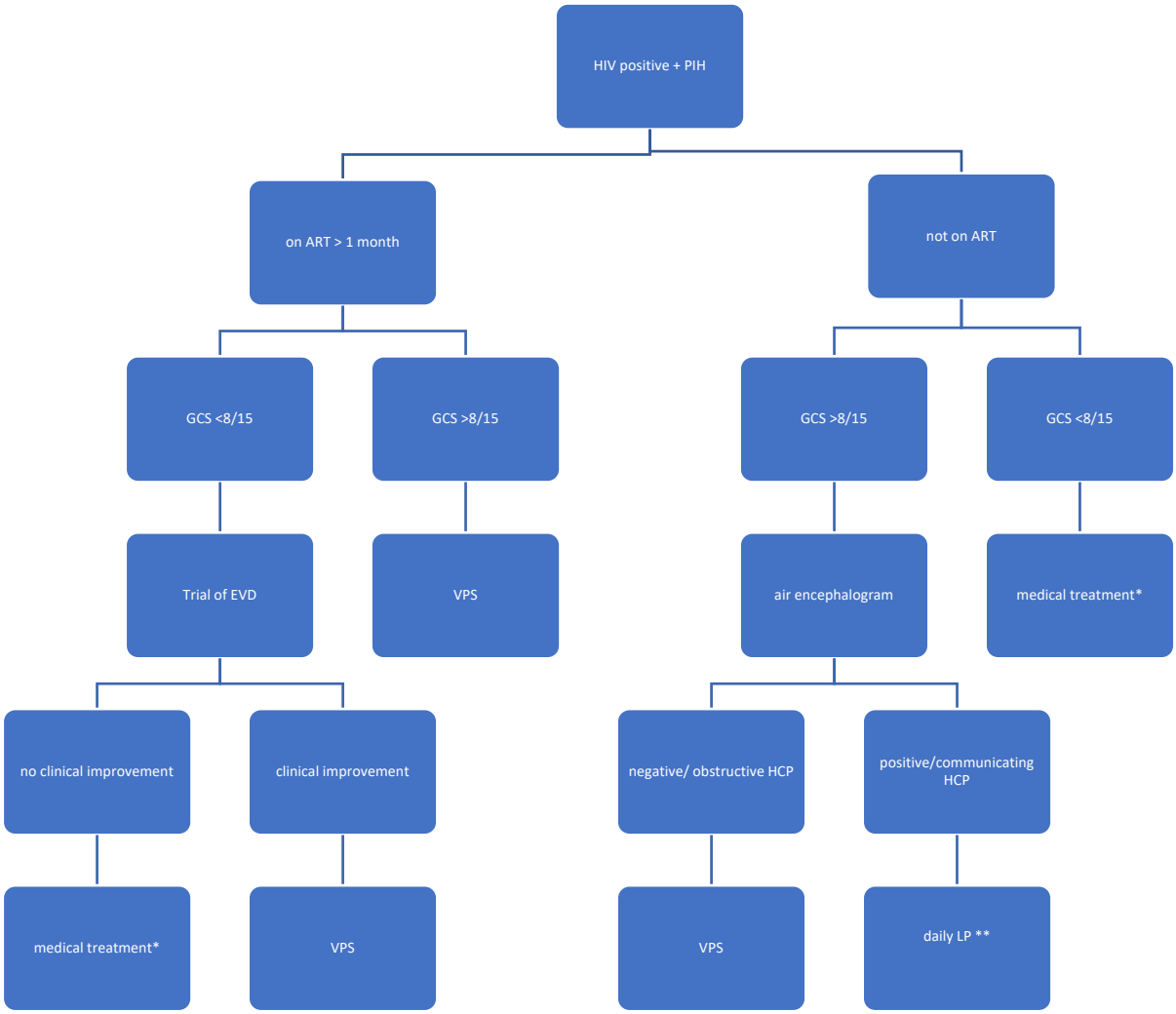

Figure 1
Proposed treatment algorithm for CSF diversion in HIV infected patients with PIH. This flow diagram aims to streamline patients who would benefit from a VPS as an index method of CSF diversion.

GCS = Glasgow Coma Scale/ EVD = External Ventricular Drain/ VPS = Ventriculoperitoneal shunt/ LP = lumbar puncture.

**best medical treatment as per protocol (including but not limited to antimicrobials)*
***daily lumbar punctures and removal of CSF as guided by opening pressures and protocols*

6. Appendices

6.1. Data collection sheet

6.2. Patient information sheet and consent form

6.3. Modified Rankin Scale

7. Ethics approval letter (DRC and HREC)

8. Instructions from SAJHIM for authors

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Neurosurgical management of Post infectious hydrocephalus in HIV infected patients: A prospective cohort study

Patient details:

Name _____

Folder Number _____

D.O.B _____

Date of admission _____

Admission criteria:

Clinically

Admitting GCS E ☐ M☐ V☐

Neurological deficits Yes☐/ No ☐ [specify]
_____

Presenting problem: headache ☐/ confusion ☐/decreased LOC ☐/seizures ☐ /other
_____

Relevant PMH: _____

Treatment initiated: antibiotics no ☐/ yes ☐ [specify]
_____

Laboratory:

Blood:

HIV status proven (ELISA)☐ / suspected☐ (first diagnosis) _____

CD4 count _____

Viral load _____

CLAT _____

Chemistry sodium _____/ protein _____ creatinine_____

CSF

Specimen sampled ventricle☐/ lumbar☐

Opening pressures _____

Polymorphonuclearcells_____/Lymphocytes_____/Erythrocytes__ _____

organism cultured _____ sensitivity _____

CSF protein_____ glucose_____ chloride_____ CSF CLAT _____

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IMAGING:

CXR _____

Head CT ☐/ MRI ☐ (pre-contrast ☐/ post-contrast ☐)

Findings: Hydrocephalus ☐/ mass lesions/ SOL ☐ [specify] _____

Basal enhancement ☐ /infarcts ☐ /Hypodensities ☐ location _____

Other Findings _____

HCP : communicating ☐ **/**non-communicating ☐ **Air Encephalogram** ☐/ **Column test** ☐

INTERVENTION

- **Medical**
  - ART regimen no☐ / yes ☐ [specify] _____
  - Therapeutic taps Duration _____
- **Surgical**
  - EVD Date _____ /Duration _____/ complications _____

- ETV Date _____
- VPS Date _____

Duration of admission _____

Repeat imaging ☐ CT ☐/MRI ☐ findings: _____

OUTCOMES

	Discharge	Month 1	Month 3	Month 6
Survival				
GOS				
mRS				

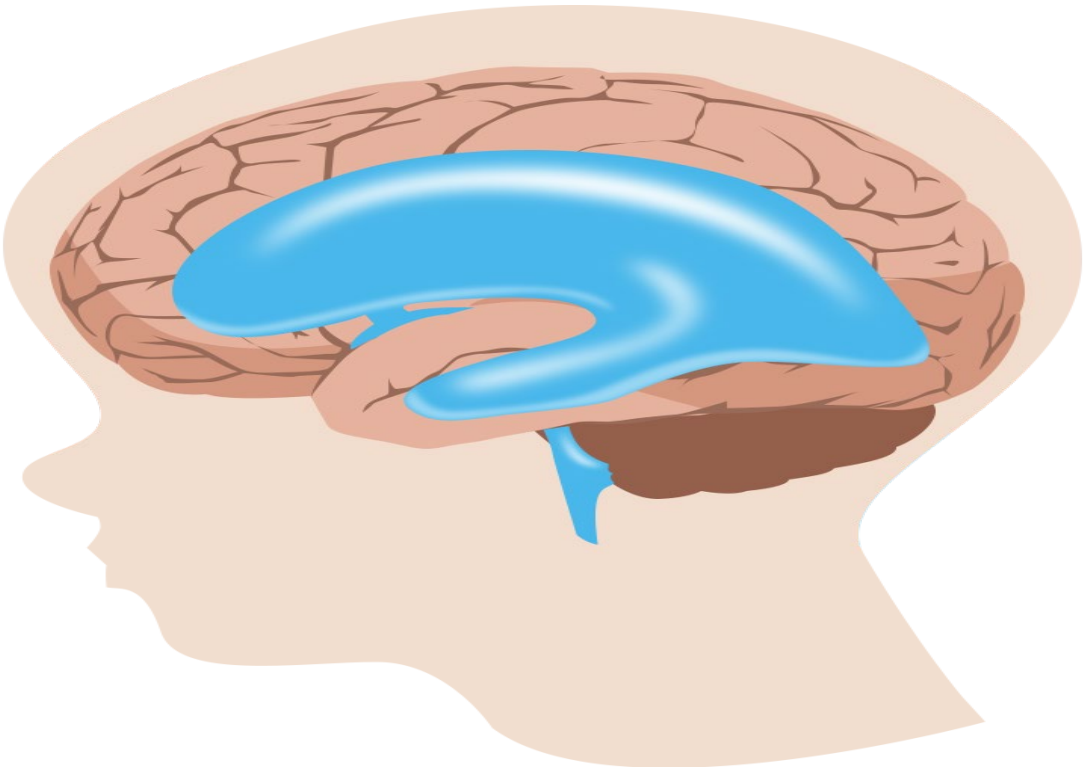
COMPLICATIONS:

- Neurological deterioration ☐
- Death ☐
- shunt dysfunction ☐
- ETV failure ☐
- Other (specify) ☐

The management of post infectious hydrocephalus in HIV infected patients.

-A prospective observational cohort study

***Patient information leaflet and Consent Form*



Primary investigator: RM Lekoloane, MBChB

Contact number: 0834936483

Email: rene.michelleL27@gmail.com

Co-investigator & Supervisor:

- AG Fieggen, MBChB MSc, MD (Neurosurgery) FCS (SA)
- SK Dlamini, MBChB, FCP (SA) Cert ID (SA)

What is research and why are we doing this particular research?

In simple words, research is what scientists do when they want to find out more about certain topics or conditions with the aim of facilitating the implementation of new therapies. In our research, we are looking for patients that are admitted to the neurosurgical services at Groote Schuur Hospital with hydrocephalus (which is accumulation of cerebrospinal fluid within the brain's ventricular channels) as a result of having had an infection to the brain. We are looking for patients that have this condition and are also HIV infected. We want to find out how well the patients are doing following admission and treatment for their condition. We want to see how well they are at 1 month, 6 month and 12 months after getting sick.

Why have I been invited to take part in this research project?

We want to check up on you following your treatment on regular/scheduled appointments to assess your progress and disability (if any). No new medications will be admitted or prescribed during this study and no new changes will be instituted for the purposes of this study. The purpose of this study is to establish how many individuals do well after they have been treated and if there any methods of treatments which work better than others. The reason why we want you to be a part of this, is that many people with the same type of condition still die all over the world, and by us understanding which methods work better we can find a way to make sure everyone gets the best treatment method.

Who is doing this research?

The research will be done at the Groote Schuur hospital by a team of doctors who will not necessarily be involved in your care whilst in the hospital but have a working relationship with the neurosurgical/ brain doctors working at Groote Schuur hospital. And as a result, they have an understanding of the care you will receive and what to asses on further check-up. The research is also educational and will be supported through the university of cape Town.

What is expected of me in this study?

During your admission to the hospital, the doctors working at the neurosurgery unit at Groote Schuur will be called for advice on how to better care for you in your condition. At this point they will decide how they want to treat your condition. What we will be doing during this time is seeing how you are on admission to the hospital, and check on what treatment the neurosurgery doctors have chosen for you and how well it has worked for you. We will also take note of how long you were admitted for and how much improvement you've made from admission, to the point of being discharged home.

While you are part of the study, the research team will be checking up on you at regular intervals like 1 month, 6 months and a year after your admission to the hospital. We want to find out how having the treatment has impacted on your daily activities.

What the risks with being in the study?

The type of study we will be doing has very little risks involved as we will not be changing your treatment or giving you any new treatment. If bad things should happen, they are most likely to be from the illness and its progression rather than taking part in this study. This study is purely from an observational point, meaning we are just documenting things that have been done by your doctors and how those treatments have worked out.

What are the benefits of being involved in the study?

The benefits of getting involved in this study is that you will have the researchers following up on your progress at the clinic appointments. As for the benefits of the study as a whole, the information collected throughout the study will help us to plan better treatment options for other people who will come to the hospitals with the same illnesses, making sure they will have better results than they are currently available.

Will anyone know that I am in the study?

Your involvement in the study will be kept a secret and by this we mean that all the things that we know about you including your personal details, your medical conditions and progresses will be kept strictly between the investigators and your doctors. The information will be protected by the researchers and will not be shared with anyone outside the study. When it comes to publishing the results of the study, we will make sure that no personal information is distributed and should we have to include personal information for whatever reason, you and your family will be asked for permission.

And what if I do not wish to participate in this study?

Fortunately, we cannot force you participate in the study and you are free to walk away at any time without fear that your medical treatment will be compromised. This is emphasized more so in that the investigators are not your treating physicians.

We do however urge you to consider the valuable information we will be able to get with your participation and the long term benefits this study will provide for future patients that present with the same condition.

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Management of Post infectious hydrocephalus in HIV infected patients: A prospective observational cohort study.

Consent form

Name of Participant:

_____

1. I consent to participate in this project, the details of which have been explained to me, and I have been provided with a written plain language statement to keep.

2. I understand that the purpose of this research is to investigate the survival outcomes of HIV infected patients with post infectious hydrocephalus following neurosurgical intervention

3. I understand that my participation in this project has no bearing on the intended treatment for my condition and that the investigators will in no way influence the type of treatment I am to receive.

4. I understand that my participation in this project is for academic research purposes only.

5. I acknowledge that the possible effects of participating in this research project have been explained to my satisfaction.

6. In this project, I will be required to attend scheduled appointments at dedicated follow up clinics following my discharge from the hospital. I understand and give permission for follow up telephonic calls and/or home visits in instances where I am unable to physically attend the scheduled visits.

7. I understand that my interviews will involve assessment of my functional state and enquiry into my personal and home life. I understand that the interviews may involve discussions with my next of kin and/or immediate relatives.

8. I understand that my participation is voluntary and that I am free to withdraw from this project anytime without explanation or prejudice and to withdraw any unprocessed data that I have provided.

9. I understand that the data from this research will be stored at the University of Cape Town's division of Neurosurgery at Groote Schuur Hospital and will be destroyed after 5 years.

10. I have been informed that the confidentiality of the information I provide will be safeguarded subject to any legal requirements; my data will be password protected and accessible only by the named researchers.

11. I understand that after I sign and return this consent form, it will be retained by the researcher.

Participant Signature: **Date:**

_____ _____

The Modified Rankin Scale (mRS)

(Use web calculator at www.modifiedrankin.com)

0 No symptoms

1 No significant disability; able to carry out all usual activities, despite some symptoms

2 Slight disability; able to look after own affairs without assistance, but unable to carry out all previous activities

3 Moderate disability; requires some help, but able to walk unassisted

4 Moderately severe disability; unable to attend to own bodily needs without assistance, and unable to walk unassisted

5 Severe disability; requires constant nursing care and attention, bedridden, incontinent 6 Dead

References:

Rankin J (May 1957). "Cerebral vascular accidents in patients over the age of 60. II. Prognosis". Scott Med J 2 (5): 200–15

Patel, N., et al. Simple and reliable determination of the modified Rankin Scale in neurosurgical and neurological patients: The mRS-9Q. Neurosurgery, published online in advance of print 26 July 2012

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021) 404 7682
Email: nosl,tsama@uct,ac,za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

20 February 2018

HREC REF: 069/ 2018

Prof G Fieggen
Division of Neurosurgery
Old Main Building

Dear Prof Fieggen

PROJECT TITLE: NEUROSURGICAL MANAGEMENT OF POST INFECTIOUS HYDROCEPHALUS IN HIV-INFECTED PATIENTS (MASTERS CANDIDATE - DR R LEKOLOANE)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee 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 28th February 2019.

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/researchh/humanethics/forms)

We acknowledge that the student Dr R Lekoloane will be Involved in this study.

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

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.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number:
FWA00001637.
Institutional Review Board (IRB)
number: IRB00001938

UNIVERSITY OF CAPE TOWN

Department of Surgery
Departmental Research Committee
Dr Timothy Pennel
D24 Office, Groote Schuur Hospital
Observatory 7925
South Africa
Tel (021) 404 3430
Email: **tim.pennel@uct.ac.za**
26 Jan 2018

Dr R Lekoloane

Department of Surgery
University of Cape Town

Dear Dr Lekoloane
RE: Project 2018/005

PROJECT TITLE: Neurosurgical Management of Post Infectious Hydrocephalus in Hiv Infected Patients. A Prospective Observational Cohort Study.

The above protocol has been reviewed by the Department of Surgery Research Committee. I am pleased to inform you that the committee approved the scientific merit of the study, and endorse the protocol for submission to the relevant ethics committee.

Although this letter serves as confirmation that the above protocol has successfully passed through the surgical DRC, respective ethics committees still require DRC chair signature before submission.

Please use the above project number in all future correspondence,

Yours sincerely

DR TIMOTHY PENNEL
CHAIRMAN: RESEARCH
ETHICS COMMITTE

INSTRUCTIONS FROM JOURNAL

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Submission status	open
Word limit	3500-5000 words (excluding the abstract, tables, figures, graphs, and references)
Abstract	maximum: 250 words requires structural headings: Background, Objectives, Method, Results and Conclusion
Callout	maximum: 50 words requires structural heading: What this study adds
Main text	requires structural headings, refer to the full structure 'Ethical considerations' is a sub-section in the manuscript and must include: • Name of the ethical review committee • Study approval number • Manner of consent (written, oral) for human participants • Description of measures taken to maintain the confidentiality of data • If the study was not human or animal research or the study was determined to be non-human subjects research or exempt, the authors must provide a statement with those details in this section.
References	60 or less, adhere to the Vancouver referencing style
Tables, figures and graphs	7 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the Formatting requirements page and the AOSIS house style guide
Compulsory supplementary file(s)	the Authorship, disclosure statements, copyright, and license agreement form, Ethical Clearance/Waiver Documentation and any other relevant form applicable to your submission
Ethical clearance/waiver documentation	evidence of ethical clearance for the study, such as the study approval letter or certificate from the Institutional Review Board (IRB), a waiver from the IRB et cetera

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Objectives, Method, Results and Conclusion.

- Background: *Why do we care about the problem?* State the context and purpose of the study. (What practical, scientific or theoretical gap is your research filling?)
- Objectives: *What problem are you trying to solve*? What is the scope of your work (e.g. is it a generalized approach or for a specific situation)? Be careful not to use too much jargon.
- Method: *How did you go about solving or making progress on the problem*? State how the study was performed and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- Results: *What is the answer*? Present the main findings (that is, as a result of completing the procedure or study, state what you have learnt, invented or created). Identify trends, relative changes or differences on answers to questions.
- Conclusion: *What are the implications of your answer*? Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)

Do not cite references and do not use abbreviations excessively in the abstract.

What this study adds: What key insights into the research results and its future function are revealed? How do these insights link to the focus and scope of the journal? It should be a concise statement of the primary contribution of the manuscript; and how it fits within the scope of the journal.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by the use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic and should clarify the knowledge gap that this study will address. Your argument should be supported by the use of evidence from the literature.

- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.