# MMed thesis:
# Guillain Barré Syndrome (GBS) in Cape Town, South Africa: a descriptive outcome cohort study

**Registrar's name:** Dr Sarvani Chetty
Student number: CHTSAR005

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**Supervisor:** Dr K. Bateman
**University of Cape Town, Faculty of Health Sciences**
**Department: Department of Medicine, Groote Schuur Hospital**

**Contact Details:** sarvani.chetty@uct.ac.za

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**Statement of contribution and declaration of authorship:**

I was actively involved in this research work as a sub-investigator in the IGOS trial at the local site in Cape Town, South Africa. My involvement included participant recruitment, consenting, collecting of data which included clinical assessment and management of patients both acutely and at follow-up assessments, completion of data forms, electrophysiological testing and CSF sampling and analysis.

I, Sarvani Chetty, hereby declare that the work on which this dissertation/thesis is based is my own 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.

Signature: ……Signed by candidate……

Date: 26 July 2019…….

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**Guillain Barré Syndrome (GBS) in Cape Town, South Africa: a descriptive outcome cohort study**

Abstract

INTRODUCTION

Guillain-Barré syndrome (GBS) or acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is an important cause of acute severe and life-threatening weakness. It occurs worldwide and may affect all age groups, but varies widely in clinical presentation, subtype, electrophysiology, course and outcome. There is sparse literature on GBS in low and middle income countries (LMIC), and the effect, if any, of HIV on GBS. This observational cohort study aims to describe the clinical presentation and outcome of acute GBS in Cape Town, South Africa, in participants recruited into the International Guillain-Barré Syndrome Outcome Study (IGOS). A secondary aim, given the high HIV prevalence in South Africa, is to describe and compare GBS participants with and without HIV infection.

METHODS

Between 1 June 2014 and 31 January 2017, we recruited participants 18 years or older presenting to Groote Schuur Hospital in Cape Town with acute GBS (< 2 weeks onset of symptoms) who were available for 1 year follow up. We recorded demographic, clinical, laboratory, electrophysiological and treatment data at entry. At follow-up at weeks 4, 26 and 52, GBS-related complications and GBS disability scale scores (GDSs) were evaluated. A good outcome was defined as the ability to walk unaided (GDSs $\leq$2) by 6 months. The clinical presentation and outcomes of HIV-uninfected and -infected participants were compared.

RESULTS:

Of 31 recruited participants, 1 participant was re-diagnosed as acute onset-CIDP and excluded from the study and 1 participant demised of an unrelated cause within the first week. 19 participants were male and the median age was 40 years. Reported antecedent infections (73%), co-morbid HIV infection (30%) and tuberculosis (15%) were frequently seen. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP; 67%) and acute motor axonal neuropathy (AMAN; 17%) were the most common phenotypes.

Overall, GBS-related complications occurred in 46% of participants. The major complication was pneumonia which occurred in 23% of the total group, and all required intubation/ventilation. Other septic complications (drip site or systemic) were less common, 6% of the entire group. At entry, 83% had GDSs >4 indicating severe disability. The ability to walk unaided was regained by 37% at 4 weeks, 75% at 6 months and 79% at 1 year. Three participants remained severely affected at 1 year (GDSs of >3).

There were no differences in antecedent infections, treatments given, or motor outcomes between HIV-infected and -uninfected GBS participants apart from a trend towards higher CSF protein in the HIV-infected group (p-value 0.05). AIDP was the most common GBS variant in both groups. AMAN was only seen in the HIV-uninfected group, whereas Miller Fisher

syndrome (MFS) was more common in the HIV-infected group. However, the numbers were too small to reach statistical significance.

CONCLUSION

Infections with HIV and tuberculosis frequently co-occurred with acute GBS, whether this reflects true disease association or merely high background disease prevalence cannot be confirmed by this study. AIDP is the most common phenotype unlike other LMIC regions such as Asia where AMAN predominates. In this cohort, 76% of participants showed good outcomes being able to walk unaided or having no/minor symptoms by 6 months. However, of the remainder only 1 showed significant recovery at 1 year. HIV participants had similar clinical presentations, complications and outcomes compared to the HIV-uninfected group. Mortality was low.

1. *Introduction and literature review:*

## *1.1 Introduction:*

Guillain-Barré syndrome (GBS) is an important cause of acute severe and life-threatening weakness that occurs worldwide and may affect all age groups. The diagnosis is considered in the presence of a combination of acute symmetrical weakness in limbs with sensory disturbances, and hypo- or areflexia, with a mild or absent cerebrospinal fluid cellular reaction despite high protein.(1) An early and accurate recognition of Guillain-Barré syndrome may be challenging.(2) Even though tests like lumbar puncture and electrodiagnostic studies can increase the level of diagnostic certainty, there are no biological markers to reliably diagnose GBS. Diagnostic uncertainty therefore makes accurate determination of incidence difficult and estimates of incidence may vary widely. Worldwide, the incidence of GBS ranges between 0.16 and 3.00 per 100 000 person –years (3) The clinical course and outcome of GBS patients varies in different geographical region. The frequency of GBS increases with age for both female and males. Males were more frequently affected than females in a ratio of 1.5:1. Worldwide, male gender and higher age are independent risk factors for developing GBS.(4) The incidence of GBS in South Africa is not known, and there is relatively scanty epidemiological data from other developing or lower and middle income countries. Whilst GBS is a relatively uncommon disease, it is important. It may cause substantial morbidity and mortality in those whom it affects, and it can be difficult to predict the outcome in individual patients. There is very limited literature on GBS in a South African context. It would be of value to describe our local experience of the clinical presentation, course and outcome of GBS and evaluate how this may compare with the established literature on GBS from other areas. The literature review that follows summarizes what is known at present about GBS pathogenesis, clinical presentation, HIV and GBS, complications, outcomes, treatment and the international cohort study; International GBS outcome study (IGOS) of which this cohort contributes towards.

## *1.2 Antecedent infections and pathogenesis:*

GBS is postulated to be an autoimmune condition triggered by a preceding infection in up to half of cases.(5) It may follow infections caused by bacterial or viral pathogens most often affecting respiratory or gastrointestinal systems. Molecular mimicry between microbial and nerve antigens is said to be a major driving force behind the development of *Campylobacter jejuni* (*C.jejuni*) associated GBS.(6) Molecular mimicry is the sharing of homologous epitopes between bacterial lipopolysaccharide and ganglioside surface components of peripheral nerves, especially on the axolemma. It is proposed that these molecular similarities, lead to an antibody response against the bacteria which also attacks neuronal axons and thereby results in GBS in some infected individuals.(7) *Campylobacter jejuni* is responsible for up to one third of cases, but other organisms such as cytomegalovirus, Epstein-Barr virus, mycoplasma, *Haemophilus influenzae*, and influenza A virus are also detected in patients with GBS.(8) There is little understanding of the interaction between microbial and host factors that permits the immune response to shift towards autoreactivity. Furthermore, it is

unknown what the role is of genetic and environmental factors that may affect an individual's susceptibility to develop GBS.(6) The burden of infectious diseases in the developing countries may influence the nature of GBS in that region. According to Islam et al (8), who conducted a case control study in Bangladesh, 57 of their 100 GBS group had positive *C.jejuni* serology. The presence of this known antecedent infective trigger is hypothesized to be more frequent in countries with a high incidence of diarrhoea and a poor hygienic infrastructure. However, despite the clear link between specific infections and GBS, the chance of developing this severe post infectious complication is very small.(7) Tam et al (9) determined that the incidence of GBS among patients with Campylobacter Infection is 1.17/1000 person-years (95% confidence interval [CI], 0.38–3.63). The risk of GBS is believed to be elevated for only ∼2 months after development of *Campylobacter* enteritis; this incidence equates to a <2/10,000 probability that a patient with *Campylobacter* enteritis will develop GBS.(10) This suggests that additional bacterial and/or host-related factors are important as well, because not all strains expressing ganglioside mimics induce GBS.(6) Seasonality has been implicated as a triggering factor. The seasonal variation in GBS, with high winter predominance in Western countries, the Middle East and Far East, but summer predominance in the Indian subcontinent and Latin America has been well established in literature. However, the association has most frequently been weak and presumably relates to seasonal fluctuations in infectious diseases.(11)

### *1.3 Clinical presentation and its variants:*

#### *1.3.1 Diagnosis:*

The need for diagnostic criteria arose when an association was discovered between GBS and the swine flu vaccination campaign of 1976–1977. In 1978, the US National Institute of Neurological Disorders and Stroke (NINDS) developed the first case definitions for GBS. It was then modified by Asbury and Cornblath in 1990 and this continues to be the most widely used criteria in clinical practice (see appendix A).(12) According to Asbury and Cornblath, the two major features that are required for the diagnosis of GBS; are progressive motor weakness and areflexia. The criteria broadly consisted of features that strongly support the diagnosis of GBS, and features that cast doubt and rule out the diagnosis.(13) More recently, the Brighton Collaboration developed a new set of case definitions for Guillain-Barré syndrome, in response to another possible link between Guillain-Barré syndrome and the H1N1 swine flu vaccination campaign of 2009/2010. The Brighton criteria identifies GBS with four levels of diagnostic certainty, from level 1 (highest) to level 4 (lowest). The Brighton criteria are not intended for clinical practice. Additional research is needed to develop criteria that can be used to swiftly diagnose GBS and its variants. (7)

#### *1.3.2 Clinical symptoms:*

GBS varies in distribution and extent of cranial nerve deficits, sensory symptoms, weakness, ataxia, pain, autonomic dysfunction, and the course of the disease. Numbness and/or paraesthesia are the usual sensory complaints. Half of patients will have cranial nerve deficits in particular bilateral facial weakness, bulbar dysfunction and extraocular muscle dysfunction.

Pain especially painful paraesthesia, backache, myalgia and meningism occur in 54-89% of GBS patients.(7) Approximately a quarter of patients develop respiratory difficulties requiring invasive ventilation. Respiratory insufficiency develops insidiously in GBS.(14) Nadir is usually reached in four weeks. Studies have shown that 80% reach nadir within two weeks and 97% reach nadir in four weeks. Progressive phase is usually followed by a plateau phase which occurs from two days to six months ( median duration one week before recovery).(2)

### *1.3.3 GBS and its variants:*

GBS is an extremely clinically diverse disorder and includes several clinically distinctive variants, formes frustes, and atypical cases. The frequency of these variants relates to the geographical area in which the disease is reported.(5)

AIDP is the most common variant of GBS in Europe and North America (60-80%).(7) AIDP is a monophasic illness defined as an acute flaccid paralysis, characterized by symmetrical weakness of the limbs, and hyporeflexia or areflexia, which reaches a maximum severity within 4 weeks. Sensory symptoms, such as paraesthesia or numbness, usually start distally and have a symmetrical pattern, which is often accompanied by cranial nerve deficits and autonomic dysfunction (NINDS criteria for AIDP in Appendix A).(7) Electrophysiological studies show typical demyelination. This suggests that the immune target in this form of GBS is within the Schwann cell surface membrane or the myelin.(5)

Axonal variants of GBS may also occur namely a pure motor variant, acute motor axonal neuropathy (AMAN), and a sensorimotor variant, acute motor and sensory axonal neuropathy (AMSAN), which may be considered a severe variant of AMAN.(7) Electrophysiological studies confirm the motor and/or axonal degeneration. AMAN is known to be triggered by enteric infection, commonly *C. jejuni* and is frequently associated with antiganglioside antibodies (GM1, GM1b, GD1a or GalNAc-GD1a) AMAN occurs more frequently in east Asia at 60-80% (China and Japan).(15)

The nodal and paranodal regions are important in the understanding of antiganglioside antibody mediated neuropathies. The axonal and demyelinating classification is ambiguous with regards to these neuropathies and therefore the term nodopathy is deemed more appropriate.(16) Nodopathies lead to disruption at the node of Ranvier with resultant transitory nerve conduction failure which may progress to axonal degeneration. In antiGM1 associated AMAN, electrophysiological studies may show conduction blocks and/or slowing that resolve without the development of excessive temporal dispersion of action potentials. Owing to this rapid recovery, the patho-mechanism of injury is thought to be caused by an impaired physiological conduction at the node of Ranvier rather than demyelination. It may therefore be recognized as a nodopathy.(16)

Miller Fisher syndrome (MFS) is another variant characterized by the triad of ophthalmoplegia, ataxia and areflexia and is associated with anti GQ1b antibodies.(17) Most of the patients with MFS present with at least two features and have supportive features like an elevated CSF protein and serum autoantibody. MFS represents 5% to 10% of GBS cases in Western countries and it is more common in Eastern Asia, accounting for up to 25% of Japanese cases. MFS usually have a good clinical outcome but some develop limb weakness

and respiratory insufficiency (termed MFS–GBS overlap syndrome). Other local variants of GBS, such as the pharyngeal–cervical–brachial (PCB) variant have also been reported. PCB manifests with ptosis, facial, pharyngeal and neck flexor weakness that spreads to upper limbs and spares the legs relative to the arms.(18) The subtypes vary globally and are dependent on trigger/antecedent risk factors. (6)

### *1.4 HIV and GBS:*

Several reviews suggest that GBS tends to occur early in HIV with high $CD_4$ counts (>500). (19) Brannagan et al described ten patients, and amongst these ten, GBS was frequently found to be the first manifestation of HIV infection, even without decline of $CD_4$ counts, at the time of seroconversion. However, 40% of their patients developed GBS after onset of AIDS and the $CD_4$ count was less than 200.(19) In a Zimbabwean study of 32 GBS patients, 55% were HIV infected, which may relate more to the background prevalence of HIV infection than to a specific association with GBS.$CD_4$ counts were not recorded in that study.(11) Whilst GBS has been reported in patients with very severe immunosuppression ($CD_4$ <50 per µL cells), an acute demyelinating polyradiculoneuropathy (AIDP) in the context of profound immunosuppression may be caused by direct cytomegalovirus infection, and this should therefore be sought and treated appropriately.(20) Diffuse infiltrative lymphocytosis syndrome (DILS) most often manifests as an acute or subacute painful sensorimotor polyneuropathy and may be an AIDP mimic. Sicca symptoms and CD8 hyperlymphocytosis are common non-specific features in DILS, but because nerve biopsy is required for a definitive diagnosis it may occasionally be difficult to separate HIV-associated GBS from severe DILS neuropathies.(19) Evidence of $CD_8$ infiltration is routinely sought after at our centre.

A few case reports have presented GBS as an immune reconstitution syndrome (IRIS) phenomenon. IRIS may develop as the 'unmasking' or paradoxical worsening of pre-existing infection in the context of immune recovery.(21) Rapid recovery of T-cell immunity in response to pre-existing antigens occurs resulting in disease manifestation or a clinical deterioration. One of the case reports was that of a male with $CD_4$ cell count of 545 cells/µL who presented with symptoms of rapidly progressing weakness, bilateral lower limb paraesthesia, and partial inability to ambulate, two months after antiretroviral initiation.(20) The other report was of a male patient with a $CD_4$ count of 31 cells/ µL who presented with neurological fallout 26 days after antiretroviral initiation.(21) The proposed underlying mechanism of IRIS depends on the degree of immune restoration following antiretroviral initiation, pre-existing antigen burden and host genetic vulnerability.(20) Cerebrospinal fluid (CSF) in HIV associated-AIDP may be atypical with a higher cellular response in the CSF: up to 50 cells per µL is still considered acceptable for diagnosis in the context of HIV. Electrophysiology is similar in both HIV and HIV uninfected cases. Treatment remains the same despite HIV infection, and includes intravenous immunoglobulin and plasmapheresis. (19)

### *1.5 Course, complications and outcomes:*

GBS is well recognized for its acute onset and heterogeneity in course and outcomes. It is associated with a favourable outcome in 80% of cases. However, mortality rates vary from

3% to 7% in regions like North America and Europe to 15% in Bangladesh.(6) In a large American based cohort study of 4954 participants recruited over 5 years, Alsheklee et al found that 88% of their patients presented with milder disease with minimal or no neurological deficits upon discharge and the in-hospital mortality rate was 2.58%.(22) According to Islam et al, outcome is worse in low income countries like Bangladesh, where 85% of patients receive no treatment, 15% die and 30% remain severely disabled.(8) Respiratory failure, cardiac arrhythmias and deep vein thrombosis are well recognized complications of GBS which may prove fatal.(6) Van den Berg et al reported on clinical outcomes in GBS after prolonged mechanical ventilation, noting that 58% of patients were able to walk unaided at six month follow up. Despite this positive outcome, almost all ventilated patients reported residual deficits (functional impairment in lower limbs 80%, 48% hands, 36% sensory deficits, 20% fatigue and pain) after follow up of two years.(23) The characteristics consistently related to poor prognostic outcome in Guillain-Barré syndrome are high age (aged 40 years and over), preceding diarrhoea (or *C jejuni* infection in the past 4 weeks), and high disability at nadir.(6) In 2005 a study reviewed how patients perceived their physical and social situation one year after GBS. Of the 90 patients evaluated from the Dutch division of an international, multicentre, double-blind, placebo-controlled trial comparing treatment with intravenous immunoglobulin (IVIg), 33% felt completely cured after one year. In this study, on assessment after one year, sensory disturbances of arms were moderately or severely reported in 22.2% of cases and 36.6% in legs. At one year evaluation, loss of power was reported in arms ( 30%) and legs (48,9%). (24)

### *1.6 Treatment:*

Several randomised controlled trials (RCT) have shown that IVIg and plasma exchange are effective immunotherapies. Although these studies were conducted in high income countries where the most common variant is AIDP.(6)Plasma exchange has been shown to be beneficial when initiated within first four weeks, however it is most effective when started early.(25) The first RCT on the use of IVIg (0.4g IVIg/kg/day for five days) was published in 1992, proving that IVIg is as effective as plasma exchange.(25) Oral steroids (or intravenous methylprednisolone 500 mg/day for five consecutive days) alone are not beneficial in GBS. (26) It is recommended that treatment is started as soon as possible in particular in patients who walk needing assistance, are bed bound or ventilated.(26) Ambulant cases of mild GBS may experience prolonged functional impairment however treatment is only recommended in those who develop additional features like autonomic disturbance, facial or bulbar weakness. (25) Miller Fisher syndrome may require supportive care only because of a relatively benign course.(26)/(25) Clinical severity of acute Bickerstaff's brainstem encephalitis and overlap with GBS suggests treatment with IVIg or plasma exchange is reasonable. (25)

## *2. Aims:*

The primary aim of this study is to describe the clinical presentation and outcomes of patients with a diagnosis of acute GBS who were admitted to Groote Schuur Hospital (GSH), Cape Town, and enrolled in IGOS.

The secondary aim is to describe and compare GBS participants with and without HIV infection.

## *3. Methods:*

This prospective observational outcome cohort was conducted by the Division of Neurology, Department of Medicine, Groote Schuur hospital, University of Cape Town between 1 June 2014 and 31 January 2017.

Groote Schuur hospital is a specialist tertiary, public health care sector hospital located in Cape Town, South Africa. It is a referring hospital for secondary hospital and clinics in Cape Town city centre and its surrounding areas, serving largely lower to middle socio-economic population who do not have medical insurance.

IGOS is a prospective multicentre, international observational outcome study collecting standardised clinical, electrophysiological and laboratory data and biosamples on participants presenting with acute GBS worldwide. The study has its coordinating centre in the Netherlands at Erasmus University and is being conducted in collaboration with the Peripheral Nerve Society and Inflammatory Neuropathy Consortium (INC). IGOS commenced enrolment in May 2012 and current enrolment is 1751 participants. Their main aim is to explore the pathogenesis of GBS and the individual clinical course, prognosis, treatment response and outcome.(27) The Neurology Division at Groote Schuur Hospital, University of Cape Town, is a participating centre in the IGOS initiative, under local investigator, Dr Kathleen Bateman, and recruited participants with acute GBS from 1 June 2014 to 31 January 2017.

While IGOS seeks to better understand GBS on a global level, this cohort aims to understand GBS in this local setting in South Africa and the effect, if any, of HIV on GBS.

### *3.1 Study population:*

Patients who fulfil the diagnostic and inclusion criteria of the IGOS study, are eligible for enrolment, provided that informed consent is obtained.

### *3.2 Inclusion criteria*:

All participants fulfilled the diagnostic criteria for GBS from the National Institute of Neurological Disorders and Stroke (NINDS; Appendix A). All patients with Miller Fisher syndrome (MFS) and other variants of GBS, including overlap syndromes were included. Participants included were age 18 yrs and older and presented to Groote Schuur hospital, Cape Town, South Africa within two weeks after onset of weakness. All participants who were willing and able to be followed up for at least one year were enrolled. Informed consent was obtained for the International Guillain-Barré Syndrome Outcome Study (IGOS) in all participants.

There were no exclusion criteria so as to limit selection bias, however participants who were misdiagnosed were excluded from further follow-up visits and relevant analyses.

### *3.3 Study data collection, procedures, outcome measures:*

Clinical data for each participant was recorded per IGOS protocol at four visits (entry, week 4, week 26 and week 52) using specific data entry forms for each visit. The clinical data sheets capture demographics, comorbidity and antecedent events. In addition, the first clinical symptoms and signs of GBS, the timing and key features of the diagnosis, neurological examination findings and the clinical course were recorded. The extent of clinical manifestations of GBS were documented in detail, including cranial nerve deficits, limb weakness, sensory deficits, ataxia, limb tendon reflexes, GBS disability scale *(Hughes et al., 1978) (Appendix C)*, pain, autonomic dysfunction, respiratory failure, and associated medical complications.(27)

Questionnaires and clinical examination for the first visit (entry) focus on potential clinical predictors of outcome, including co-morbidities and antecedent infections (upper respiratory tract infection, cold, gastroenteritis, urinary tract infection, vaccination, surgery). The presence of pain is noted and characterised, MRC sum score, reflexes, ataxia, autonomic dysfunction, cerebrospinal fluid (CSF) protein and leukocytes were captured. GBS disability score was recorded at each follow up.

Questionnaires and clinical examination for weeks 4, 26 and 52 focus on the above as well as the presence of complications (pneumonia, sepsis, deep vein thrombosis, pulmonary embolism, pressure ulcer) and GBS disability scores. Transition to chronic inflammatory demyelinating polyneuropathy (CIDP) is also recorded.

Voluntary HIV testing is offered routinely to all patients attending the Neurology Division at Groote Schuur Hospital presenting with a suspected inflammatory neuropathy, and patients undergoing testing are provided suitable pre- and post-test counselling.

Electrophysiology tests were performed within the first or second week of admission. The tests were classified according to the Hadden criteria (*Appendix D).*

### 3.4 *Data analysis:*

All clinical data was collated and analysed. Clinical factors such as clinical variants, age of onset, CSF parameters, GBS disability score at follow up, treatment options, antecedent triggers, seasonal variation, number of participants requiring ICU admission and ventilation and number of HIV infected vs non-infected participants are tabulated below.

Data was entered into an excel database for analysis using STATA version 14.1 (Texas, USA). Categorical variables were expressed as proportions while numerical variables were described using mean (standard deviations) or medians (interquartile ranges) depending on the normality of the data. The Chi square test was used to compare proportions, medians and means. A Chi square test for trend was used to compare GDS scores over time between HIV-infected and -uninfected participants. A p-value of $<0.05$ was considered to be significant.

*4. Ethical approval:*

The original study was approved in 2014 (HREC REF: (267/2014)). The permission to do this research as a sub-study towards an MMed degree was approved by the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (HREC REF:852/2017). Please see Appendix B.

*5. Results:*

*5.1 Demographic, clinical features and laboratory investigations:*

31 participants were recruited within the time period 1 June 2014 and 31 January 2017. One death was recorded at week one in intensive care unit (ICU). One patient's diagnosis was amended to acute onset chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). During her admission, on repeated history-taking, this patient described a prior episode of 'acute GBS' requiring hospitalization at a secondary hospital as well as multiple self-limited relapses since her first episode of polyneuropathy. She responded to treatment with steroids and immunosuppressants, but suffered a further relapse in the course of the next year. Her diagnosis was revised therefore to CIDP and she was excluded from further IGOS follow-up. 29 participants therefore had further follow-up data obtained. One year follow up was conducted in 83 % of participants and 79% had a six month follow up.

63% participants were male and the median age was 39 years. 57% participants were of mixed African ancestry, and 37% were black African. Reported antecedent infections were found in 73% of cases, upper respiratory tract infections (URTIs) in 46% and acute gastroenteritis (AGE) in 27%. Co-morbid HIV infection was found in 30%, tuberculosis 15% and neurosyphilis in 3% of cases. Co-morbid medical diseases found in 18 % patients, of which 6% participants suffered from Diabetes mellitus.

If a history of antecedent infection was present, median days from infection to symptom onset was 10.5 days (IQR 7-17.5). Nadir was reached by 72% at enrolment which by defined inclusion criteria needed to occur within two weeks of symptom onset. GBS occurred in winter in 47% of cases. AIDP (67%) and AMAN (17%) were the most common phenotypes. Miller Fisher or Miller Fisher overlap was found in 13% of cases with one case a PCB variant. The mean CSF protein was 0.88 g/dL (standard deviation (SD) = 0.58) and the mean CSF leucocyte was 5.58 cells/$\mu L$ (SD = 12.63).

See Table 1 for demographic, clinical and laboratory features:

| Demographics, n (%) | All (n=30) | HIV + (n=9) | HIV – (n=21) | p-value * |
|---|---|---|---|---|
| Male sex | 19 (63) | 4 (44) | 15(71) | 0.25 |
| Age in years, mean (± SD) | 39 (14.2) | 40 (8) | 39 (16) | 0.86 |
| Ethnicity | | | | |
| African | 11 (37) | 8 (89) | 3 (14) | <0.001 |
| European ancestry | 1 (3) | 0 | 1 (5) | - |
| Mixed African ancestry | 18 (60) | 1 (11) | 17 (81) | - |
| Co-morbid infections | | | | |
| HIV | 9 (30) | - | - | - |
| TB | 5 (17) | - | - | - |
| Syphilis | 1 (3) | - | - | - |
| None | 19 (63) | - | - | - |
| Antecedent infection | | | | |
| URTI | 14 (46) | 4 (45) | 10 (48) | 0.96 |
| AGE | 8 (27) | 3 (33) | 5 (23) | 0.54 |
| None | 8 (27) | 2 (22) | 6 (29) | - |
| GBS variants | | | | |
| AIDP | 20 (67) | 6 (67) | 14 (67) | 0.22 |
| AMAN | 5 (17) | 0 | 5 (24) | - |
| MFS or MFS overlap | 4 (13) | 2 (22) | 2 (9) | - |
| PCB | 1 (3) | 1 (11) | 0 | - |
| Lab investigations : | | | | |
| Serology | | | | |
| CD4, cells/μL, mean (±SD) | | 304 (242) | | |
| CSF | | | | |
| CSF Protein g/dL, median (IQR) | 0.65 (0.42 – 1.33) | 1.40 (0.70 – 1.90) | 0.60 (0.40 – 0.90) | 0.05 |
| CSF Leucocytes cells/ μL, median (IQR) | 5.58 (0-5.50) | 2.00 (1.00-7.00) | 1.00(0-4.00) | 0.26 |

**Table 1: Baseline characteristics**

* Chi square test used to calculate p-value

TB – Tuberculosis, URTI - upper respiratory tract infection, AGE – acute gastroenteritis AIDP – acute inflammatory demyelinating polyneuropathy, AMAN – acute motor axonal neuropathy, MFS – Miller Fisher syndrome, PCB – pharyngeal-cervical-brachial variant

*5.2 Treatment, complications and outcomes:*

IVIG was administered in 47% participants with no adverse effects. 30% required IVIG with neuropathic analgesics and 4 participants (13 %) did not receive any treatment.

Pain was present in 52% of participants on entry, and a greater proportion of participants reported pain at entry than at any other visit. Nevertheless, 79% of participants reported pain at some point in their course. The most common types of pain reported were muscle pain (27%) and distal paraesthesia (27%).

Overall, GBS-related complications occurred in 46% of participants. The major complication was pneumonia which occurred in 23% of the total group, and all required intubation/ventilation with 30% requiring ICU care. Other septic complications (drip site or systemic) were less common, 6% of the entire group. No complications were found in 54% of participants.

At entry 83% had GDSs >4 indicating severe disability. Ability to walk unaided (or GDS ≥3) was regained by 38% at 4 weeks, 76% at 6 months and 79% at 1 year (see figure 1). Three participants remained severely affected at 1 year (GDSs of >3). One participant died during the cohort. The cause of the one death was considered unrelated to her GBS admission: she developed massive spontaneous intrahepatic haemorrhage secondary to a presumed adenoma. Repeated attempts at hepatic artery embolization were unsuccessful and she developed multiorgan failure and demised.

See Table 2 for treatment, complications and outcomes:

| Treatment, n (%) | All (n=30) | HIV+ (n=9) | HIV – (n=21) | p-value* |
|---|---|---|---|---|
| IVIG | 14 (47) | 4 (45) | 10 (48) | 0.87 |
| IVIG + Neuropathic analgesics | 9 (30) | 3 (33) | 6 (29) | 0.79 |
| Neuropathic analgesics | 3 (10) | 2 (22) | 1 (5) | 0.14 |
| PE | 0 | - | - | - |
| None | 4 (13) | - | - | - |
| Complications | | | | |
| None | 19 (63) | - | - | - |
| Pneumonia | 8 (27) | - | - | - |
| Sepsis | 2 (7) | - | - | - |
| Other | 6 (20) | | | |
| Outcomes | | | | |
| Intubation | 7 (23) | 3 (33) | 4 (19) | 0.64 |
| ICU | 9 (30) | 4 (44) | 5 (24) | 0.39 |
| Death | 1 (3) | 0 | 1(5) | 0.51 |

**Table 2: Treatment, complications and outcomes of participants**

* Chi square test used to calculate p-value

IVIG – intravenous immunoglobulin, PE – plasma exchange, ICU – intensive care unit

sepsis – drip site and/or systemic

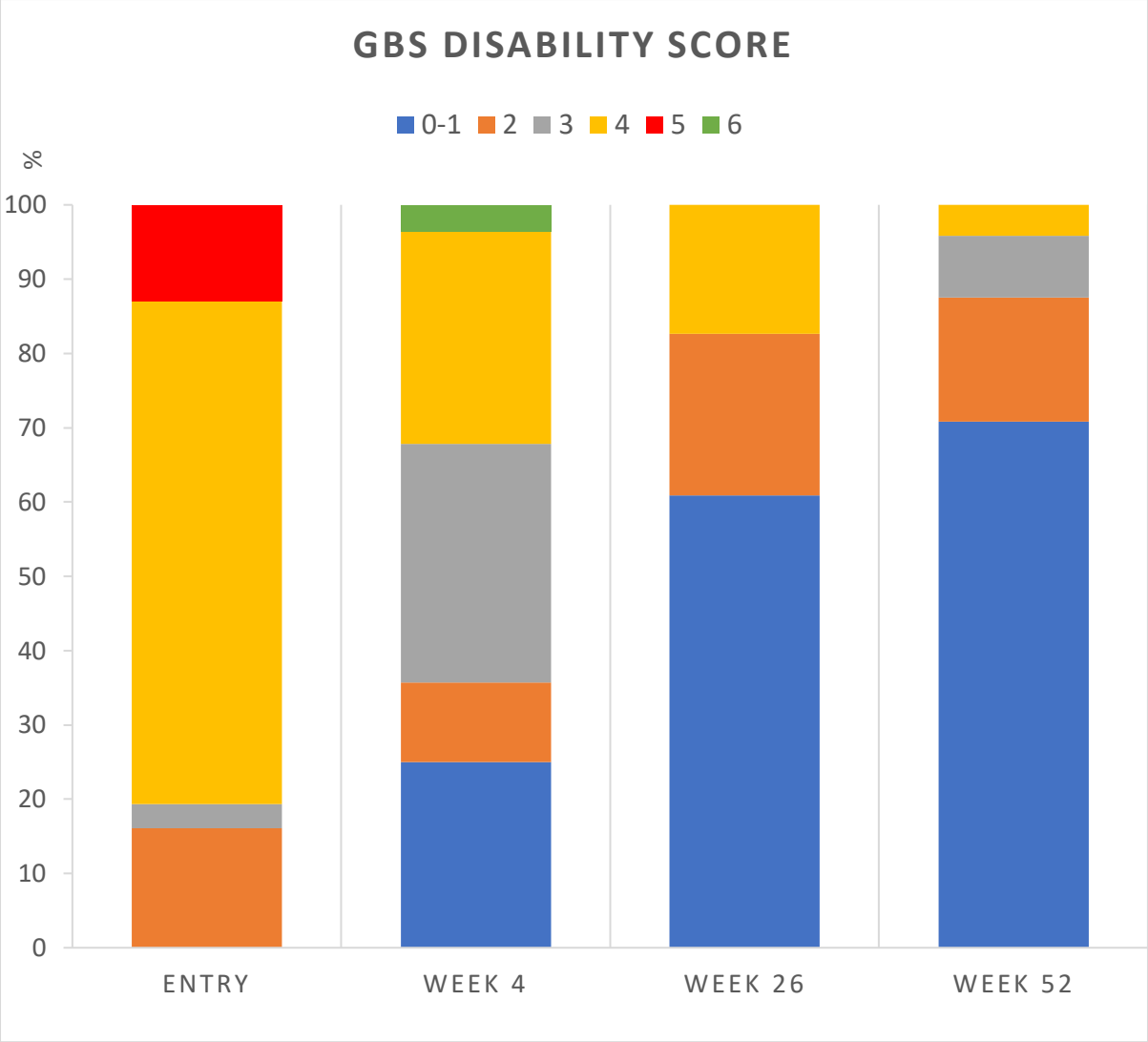


**Figure 1: GBS disability scores at follow up:** 0 - A healthy state. 1 - Minor symptoms and capable of running. 2 - Able to walk 10 metres or more without assistance but unable to run. 3 - Able to walk 10 metres across an open space with help. 4 -Bedridden or chair bound. 5 -Requiring assisted ventilation for at least part of the day. 6 -Dead

*5.3 GBS and HIV infection:*

See table 1 for comparison between HIV-infected and uninfected participants.

Nine HIV-associated GBS participants were recorded. Proportionally in this cohort more females than males (45.5% vs 21%) were HIV-infected. Age was similarly reflected in the two groups, the overall mean age was 39 years. More black African participants were noted in the HIV-infected (89%) than in the -uninfected group, with statistical significance (p–value < 0.001). The HIV-infected and -uninfected groups had similar rates of antecedent infections; upper respiratory infection (URTI) (45% and 48% respectively), whilst acute gastroenteritis (AGE) occurred in 33% HIV- infected patients and 23% in HIV-uninfected patients. AIDP was the most common GBS variant in both groups. However more HIV-infected participants had

Miller Fisher syndrome (MFS) or MFS overlap (22%) than HIV-uninfected (9%) and the only pharyngeal-cervical-brachial variant (PCB) was HIV-infected. Unfortunately our numbers are too small to reach any statistical significance.
Of note, no AMAN variants were recorded in the HIV-infected group.

In the HIV-infected group, the mean $CD_4$ was $CD_4$ 304 cells/μL (SD = 242). A statistical trend was noted towards higher CSF protein in HIV infection (p-value 0.05). More HIV-infected participants (88%) were unable to walk at entry compared to HIV-uninfected group (68%). However this did not reach statistical significance. At 52 weeks the inability to walk was similar in HIV-infected (11%) and uninfected (9%) groups; see Figure 2. HIV-infected GBS cases received similar treatment modalities as uninfected GBS patients namely; IVIG alone in 45% of cases, IVIG with neuropathic agents in 33% and 22% received neuropathic agents alone. Intubation (33%) and ICU admission (44%) were similarly needed in HIV-infected participants. No deaths were recorded in the HIV-infected GBS patients.

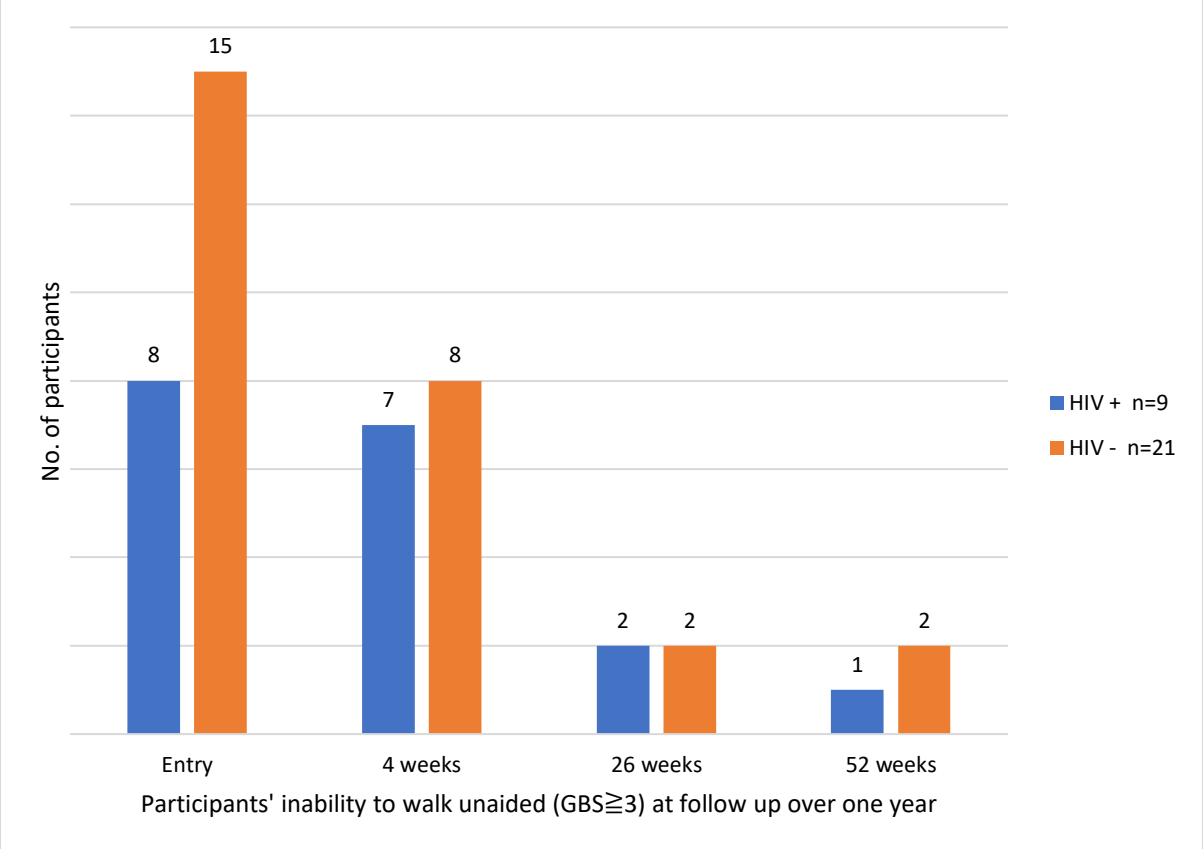


**Figure 2: Inability to walk unaided (GDSs ≥ 3) and HIV status during follow-up:**
Chi square for trend p-value 0.68. No – number GDS – GBS disability score

## *6. Discussion:*

This study highlights the clinical presentation and outcomes of GBS in a low to middle income country (LMIC) like South Africa. Of the 29 participants that were finally evaluated, good follow up was achieved with a one year follow up in 83 % of participants and 79% at six month follow up. The main findings were that AIDP was the most common phenotype in our cohort. Comorbid infections like HIV and TB co-occurred frequently. The HIV-associated GBS participants' had a mean $CD_4$ 304 (SD = 242) cells/μL. A favourable outcome, namely being able to walk unaided or having no/minor symptoms by six months, was obtained in 76% of participants. Mortality was low with one death reported in this cohort. Although, the cause of death (massive spontaneous intrahepatic haemorrhage secondary to a presumed adenoma) was entirely unrelated to GBS as already described.

In this cohort, 73% reported antecedent infections with the majority being URTI (46%). A high rate of co-morbid HIV infection was noted (30%) and tuberculosis (15%). This differs from other LMIC like Bangladesh where 46% of their participants reported antecedent infection, predominantly diarrhoea with only a few cases reporting respiratory infection. GBS in Bangladesh is frequently preceded by an enteric infection, *Campylobacter jejuni.(28)* The antecedent infection rate in this cohort was similarly reflected in systematic literature reviews such as McGrogan *et al.(17)* in which 40–70% of cases recorded an infection before onset with 22–53% having an upper respiratory tract infection and 6–26% a gastrointestinal infection.(17) Unlike this study where the mean age is 39 years, a number of studies have commented on a bimodal pattern of incidence by age, with peaks occurring in young adults and the elderly.(17)

It is notable that AIDP (67%) was the most common phenotype in our study with AMAN present in far fewer participants (17%). This is in keeping with literature from North America and Europe where demyelinating GBS is present in 60-80% of North-American and European patients.(7) Axonal GBS has been reported in 3-17% in Europe, in 23-65% in Asia(15) and in 67% in Bangladesh.(8) In a Bangladesh cohort where AMSAN (58%) was the predominant type; AMAN, AIDP and MLF constituted 28%, 10% and 4 % of their study group respectively.(28) This difference in presentation compared to Bangladesh may relate to the difference in antecedent infection with *C. jejuni,* which is known to be associated with axonal GBS. The frequency of MFS varies widely in different regions from 3% in Europe to 34% in Eastern Asia.(29) MFS was also present in the minority of cases (13%) in our cohort, but was more frequently seen than in Europe.

Co-morbid infections like HIV and TB were found in 44% of our participants. South Africa has the largest HIV epidemic. According to Statistics SA (www.statssa.gov.za) July 2018, the estimated overall HIV prevalence rate is approximately 13,1% among the South African population. The total number of people living with HIV is estimated at approximately 7,52 million in 2018. In 2017 HIV prevalence in Western Cape was at 12.6%. For adults aged 15–49 years, an estimated 19% of the population is HIV-positive. The reason for a high rate of HIV co-infection in our cohort may be a chance finding reflective of a high prevalence of these infections in the general population. However, it may be that these infections are implicated

in GBS pathogenesis. A previous study from this region by Henning *et al.* estimated more than 18 times higher incidence of GBS in HIV-infected people than in those -uninfected with HIV.(30) Accurate epidemiological data to answer this observation is not available for South Africa.

We saw no significant differences between HIV-infected and HIV-uninfected participants in terms of antecedent infections. The HIV positive group had no AMAN cases and more MFS, but this did not reach clinical significance. A non-significant difference was a higher CSF protein in HIV-infected patients (p=0.05). This is not unexpected as HIV-infected patients may have a raised CSF protein, owing to HIV infection.(19) In HIV, GBS is thought to occur more frequently in the context of a preserved rather than a depleted $CD_4$ count, and this was evident in our cohort where the mean $CD_4$ count 304 (SD = 242) cells/μL was relatively preserved. (19)The inability to walk was noted in 88% HIV-infected participants compared to 68% HIV-uninfected participants at entry, However, this did not reach statistical significance. At one year the inability to walk was similar in HIV-infected (11%) and uninfected (9%) groups, and the rate of recovery did not differ between groups. This observation is consistent with previous reports noting that HIV-infected GBS patients respond to treatment and recover spontaneously in a similar fashion to HIV-uninfected GBS patients.(19) Treatment therefore does not differ on the basis of HIV serostatus, and includes use of plasmapheresis and intravenous immunoglobulin. (19) In 2003, Schleicher *et al.* performed a retrospective review of 13 patients admitted to two tertiary academic hospitals in Johannesburg, South Africa (seven were HIV negative and six were HIV positive). Their aim was to determine the effect of HIV on ICU outcome in patients with GBS. The HIV-seropositive and seronegative had similar clinical presentations and severity of disease. The HIV-positive tended to be younger (34.5 vs 47 years of age) and included more men than in the HIV-negative group. However, these differences were not statistically significant. The mean $CD_4$ 322.5 cells/μL is similar to our cohort. The study revealed a similar ICU outcome between HIV-infected and uninfected groups especially if $CD_4$ count is greater than 200 cells/μL. A low $CD_4$ count was thought to be associated with a poor outcome as the one death reported in this study was an HIV-infected participant with a $CD_4$ 46 cells/μL, who died from severe sepsis.(31)

TB was the second most common co-morbid infection in this study. In addition to the HIV pandemic, South Africa also has the highest tuberculosis incidence globally (781/100,000).(32) *TBFacts.org* state that the highest TB Incidence rates in South Africa occur in the provinces Eastern Cape, KwaZulu-Natal and the Western Cape with 692, 685 and 681 per 100,000 respectively for 2015. The burden of TB differs with age and peaks in TB notification rates in the HIV-uninfected population occurs at ages 0−5, 20−24, and 45−49 years. In the HIV-infected population, however, there is little disparity in age.(33) As a result of the high incidence of TB in the Western Cape, it is not unexpected to find a high rate of TB comorbidity in our GBS cohort (15% of participants). In a local study from Tygerberg hospital, Cape Town, South Africa; Henning *et al.* sought to determine the validity of an association between Neuromyelitis optica (NMO) and active pulmonary tuberculosis (TB).(34) The control group comprised of hospitalized GBS patients. Two of the 14 controls (14%) were diagnosed with TB during hospitalisation, one had active PTB and the other had TB adenitis without pulmonary involvement. All participants were screened for HIV, six patients were seropositive. The prevalence of HIV infectivity was not significantly different between the cases and controls (p=0.089). (34) The incidence of TB in GBS reported in their study, also

performed in the Western Cape, is similar to that in our cohort. A few case studies in Asia have also described comorbid TB and GBS, namely two reported cases in Sri Lanka(35) and one case in Singapore.(36) It is unclear how TB may affect GBS disease. The co-occurrence of TB with GBS could be incidental in these endemic areas. However, GBS might be an autoimmune reaction to tuberculous bacilli or GBS may be misdiagnosed in cases of direct tuberculous nerve root involvement. Microbiological confirmation of tubercle bacilli in GBS can be challenging. This may be due to GBS associated respiratory muscle weakness leading to difficulty obtaining sputum for culture and may be due to a low diagnostic sensitivity of cerebrospinal fluid.(36)

In this study, recovery in the ability to walk was used as a surrogate for a favourable outcome and it was obtained using the validated GBS disability scoring system. At entry, 83% had GDSs >4 indicating severe disability. The ability to walk unaided was regained by 38% at 4 weeks, 76% at 6 months and 79% at 1 year. Three participants remained severely affected at 1 year (GDSs of >3). Our cohort showed similar, if slightly worse, outcomes to a cohort of 397 patients reported by Walgaard *et al* in 2011 (37) in which 50% had a poor outcome at 4 weeks 30% at 3 months, and 19% at 6 months after hospital admission.(37)

It is well recognized that complications may occur in GBS. In this cohort, GBS-related complications occurred in 46% of participants with pneumonia and intubation/ventilation (23%) being the most common. A similar rate of intubation and ventilation requirements were recorded in this cohort as compared to literature where 20–30% of patients develop respiratory failure and need ventilation at an intensive care unit (ICU).(6) The 3% mortality rate found in this cohort is not reflective of other works as the cause of the one death is clearly unrelated to GBS and its complications. Van den Berg et al in 2013 described mortality in Guillain-Barré syndrome and they found a relatively low mortality rate of 2.8% in the first 6 months and 3.9% in the first year.(29) It was found to be influenced by the high number of patients receiving IVIG or plasma exchange (96%) and the high number of patients not requiring support in ICUs (72%). Risk factors for death were older age, severity of weakness at entry mechanical ventilation, delay from onset of weakness to entry. In the acute phase, patients died of cardiovascular and autonomic complications. However, during the recovery phase, after neurologic improvement, two- thirds of the GBS patients, died from pulmonary infections or cardiovascular complications.(29)

In this cohort, patients with acute GBS, were offered treatments consistent with international guidelines.(38) IVIG alone was administered in 47% and IVIG with agents for neuropathic pain in 30% of participants. Four out of 29 participants did not require treatment. Pain management in our cohort appears inadequate: a high proportion (79%) of participants reported pain at some point in their course but only 29% were recorded as receiving neuropathic pain therapy with their IVIG. The reasons for this mismatch are not clear, but may relate to the timing of when participants treatment records were evaluated for study purposes. Nevertheless, this observation underscores the fact that pain occurs frequently in GBS and treatment of pain should not be overlooked.

Here we have described the clinical manifestations, treatment and outcome of GBS in our local setting of Cape Town South Africa. This study has again highlighted a high rate of co-

morbid HIV and TB. It would be of scientific interest and potential clinical relevance in areas of high prevalence to elucidate the role of these infections in GBS. However, from this small cohort, there appears to be no significant difference in GBS in HIV-infected versus -uninfected people. This study confirms that it remains appropriate to use current treatment regimens for GBS irrespective of HIV status in our local context.

### *7. Limitations*

This study has a limited number of participants and the selection bias is another factor to note. The participants were recruited from a single academic hospital rather than a population or primary health base, and so may not truly reflect the population of Western Cape.

IGOS stipulated a two week inclusion criteria. This may have excluded slower onset cases who achieve nadir in less than four weeks as per diagnostic criteria.

### *8. Conflict of interest*

The author affirm that this study and its interpretations were not under any financial or otherwise competing interest.

### *9. Conclusion:*

In this cohort, infections like HIV and TB frequently co-occurred in GBS. It is unclear if this is due to a valid disease association or rather a reflection of the high background prevalence of HIV and TB in the Western Cape. AIDP was the most common phenotype unlike other LMIC regions such as Asia where AMAN predominates. We observed similar presentation and outcomes of GBS in HIV-infected versus HIV-uninfected participants and our mortality rate was low.

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*Appendix A:*

*Asbury and Cornblath Diagnostic criteria:*

Required features

- Progressive weakness in both arms and legs
- Areflexia (or hyporeflexia).

Features supportive of diagnosis

- Progression of symptoms over days to 4 weeks
- Relative symmetry
- Mild sensory signs or symptoms
- Cranial nerve involvement, especially bilateral facial weakness
- Recovery beginning 2 to 4 weeks after progression ceases
- Autonomic dysfunction
- Absence of fever at onset
- Typical CSF (albuminocytologic dissociation)
- EMG/nerve conduction studies (characteristic signs of a demyelinating process in the peripheral nerves)

Features casting doubt on the diagnosis

- Asymmetrical weakness
- Persistent bladder and bowel dysfunction
- Bladder or bowel dysfunction at onset
- >50 mononuclear leukocytes/uL or presence of polymorphonuclear leukocytes in CSF
- Distinct sensory level.

Features that rule out the diagnosis

- Hexacarbon abuse
- Abnormal porphyrin metabolism
- Recent diphtheria infection
- Lead intoxication
- Other similar conditions: poliomyelitis, botulism, hysterical paralysis, toxic neuropathy.

Reference:

Adapted from Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27 Suppl:S21-4

*NINDS:*

NINDS Diagnostic criteria for Guillian Barré Syndrome:

Features required for diagnosis

- Progressive weakness in both arms and legs (might start with weakness only in the legs)
- Areflexia (or decreased tendon reflexes)

Features that strongly support diagnosis

- Progression of symptoms over days to 4 weeks
- Relative symmetry of symptoms
- Mild sensory symptoms or signs
- Cranial nerve involvement, especially bilateral weakness of facial muscles
- Autonomic dysfunction
- Pain (often present)
- High concentration of protein in CSF
- Typical electrodiagnostic features

Features that should raise doubt about the diagnosis

- Severe pulmonary dysfunction with limited limb weakness at onset
- Severe sensory signs with limited weakness at onset
- Bladder or bowel dysfunction at onset
- Fever at onset
- Sharp sensory level
- Slow progression with limited weakness without respiratory involvement (consider subacute
- inflammatory demyelinating polyneuropathy or CIDP)
- Marked persistent asymmetry of weakness
- Persistent bladder or bowel dysfunction
- Increased number of mononuclear cells in CSF (>50×10E6/L)
- Polymorphonuclear cells in CSF

Reference:

Adapted from Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27 Suppl:S21-4

Diagnostic criteria for Miller Fisher Syndrome (MFS)

Features required for diagnosis

- Bilateral ophthalmoparesis or ophthalmoplegia
- Ataxia
- Areflexia (or decreased tendon reflexes)
- Features that support diagnosis
- Progression of symptoms over days to 4 weeks
- Relative symmetry of symptoms
- Mild limb weakness (in case of prominent limb weakness, consider GBS-MFS overlap syndrome)
- Mild sensory symptoms or signs (in case of prominent sensory symptoms or signs, consider GBS-MFS overlap syndrome)

- Facial palsy and/or bulbar palsy
- Presence of serum IgG antibodies against ganglioside GQ1b
- Nerve conduction studies: no changes in extremities
- High concentration of protein in CSF, cytoalbuminologic dissociation

<u>Features that should raise doubt about the diagnosis</u>

- Alterations in consciousness
- Corticospinal tract signs
- Fever at onset
- Marked persistent asymmetry of weakness

Reference:

Adapted from Sejvar JJ, Kohl KS. Guillain-Barré syndrome and Fisher syndrome: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2011;29:599-612 and van der Meché FGA, van Doorn PA. Diagnostic and Classification Criteria for the Guillain-Barré Syndrome. Eur Neurol 2001;45:133-139.

*<u>Appendix B:</u>*

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: noel.lierse@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

05 December 2017

**HREC REF: 852/2017**

**Dr K Bateman**
E8, Neurology
NGSH

Dear Dr Bateman

**PROJECT TITLE: GUILLAIN BARRE SYNDROM (GSB) IN CAPE TOWN, SOUTH AFRICA: A DESCRIPTIVE, OUTCOME COHORT STUDY- LINKED TO 852/2017 (FC-candidate-Dr S Chetty)**

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 30th November 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 S Chetty 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

signature removed to avoid exposure online

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

HREC 852/2017

*Appendix C: GBS disability score*

The GBS disability score has 7 scores for disability, ranging from a healthy state to dead:

1. 0 A healthy state
2. 1 Minor symptoms and capable of running
3. 2 Able to walk 10 metres or more without assistance but unable to run
4. 3 Able to walk 10 metres across an open space with help
5. 4 Bedridden or chair bound
6. 5 Requiring assisted ventilation for at least part of the day
7. 6 Dead

Reference

Adapted from Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial prednisolone in acute polyneuropathy. Lancet 1978;2:750-3.

Appendix D:

*Hadden criteria:*

1. Normal
(All the following in all nerves tested) DML 5100% ULN
F wave present with latency *5* 100% ULN MCV 2100% LLN
dCMAP 2100% LLN
pCMAP 2100% LLN
pCMAP/dCMAP ratio >0.5

2. Primary demyelinating
(At least one of the following in each of at least two nerves, or at least two of the following in one nerve if all others inexcitable and dCMAP 210% LLN) MCV <90% LLN (85% if dCMAP <50% LLN) DML >110% ULN (120% if dCMAP <loo% LLN) pCMAP/dCMAP ratio <0.5 and dCMAP 2 2 0 % LLN F-response latency >120% ULN

*3.* Primary axonal
None of the above features of demyelination in any nerve (except one demyelinating feature allowed in one nerve if dCMAP <lo% LLN), and dCMAP <80% LLN in at least two nerves

*4.* Inexcitable dCMAP absent in all nerves (or present in only one nerve with dCMAP <lo% LLN)

5. Equivocal
Does not exactly fit criteria for any other group

"Modified from Ho and colleague.

DML = distal motor latency; ULN = upper limit of normal; MCV = motor conduction velocity; LLN = lower limit of normal; dCMAP = compound muscle action potential amplitude after distal stimulation; pCMAP = compound muscle action potential amplitude after proximal stimulation.

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