THE FREQUENCY OF HIV IN PATIENTS WITH NEWLY DIAGNOSED BELL'S PALSY AT A TERTIARY CENTRE

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of Master of Medicine in the division of Neurology

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I. DECLARATION

I, Jan Christoffel Visagie, do hereby declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the division of Neurology, University of the Witwatersrand, Johannesburg. This research report is submitted in the publishable format as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other University.

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The …2nd… day of …May… 2023

II. DEDICATION

To my wife, Amanda, for your loving support and patience in challenging times and for dreaming with me.

To my daughter, Alyssa, for unconditional love and inspiration.

To my parents, Jan, Anton, Marié and Sanneke, for being examples of perseverance, dedication and faith and for never doubting me and my dreams.

In memory of my twin sister, Marilette, for having been my biggest supporter and having shared all my victories since the day we were born. You are forever in my heart and thoughts, and all my victories are still yours.

III. PUBLICATIONS AND PRESENTATIONS ORIGINATING FROM THIS RESEARCH

Oral presentation at the Congress of the Neurological Association of South Africa (NASA), Cape Town, 6 May 2023.

IV. ETHICAL CONSIDERATIONS

Permission for this prospective study was obtained from the CEOs of each of the respective hospitals at which the study was conducted (CMJAH, CHBAH, HJH) as well as the Human Research Ethics Committee (HREC) of the University of Witwatersrand (clearance number – M191137).

v. ABSTRACT

Background: Bell's palsy is the most common disease affecting the facial nerve and presents with unilateral lower motor neuron (LMN) facial weakness. An immunologically-mediated pathophysiological process is suspected, with a viral pathogen being one of the possible precipitating factors. The exact cause is however still unknown, with numerous associated diseases that have been described, one of which is HIV, with facial palsy being the most common cranial neuropathy in HIV.

Aims: To describe the sociodemographic characteristics and frequency of HIV in patients with newly diagnosed Bell's palsy. Furthermore, to determine the mean CD4 and viral load of the HIV positive subgroup.

Methods: This retrospective-prospective observational and descriptive study evaluated 58 adult patients (18 years and older) that presented with atraumatic LMN facial weakness (Bell's palsy) between January 2019 and November 2021 at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH). Data was obtained from patients' files and prospective patient interviews and annotated on data capturing sheets. It included demographic information, date of diagnosis of Bell's and side of the face involved, as well as the HIV status and the CD4/Viral Load (VL) for all HIV positive patients. Furthermore, the HbA1c, TPHA/RPR and ANA tests were also obtained. Descriptive statistics were used to determine the frequency of HIV. For continuous variables (CD4/VL), the mean and standard deviation were determined for normally distributed data, whereas the median and interquartile range were determined for data not normally distributed. This was subsequently presented in a tabulated format.

Results: Of the 58 patients included, the mean age was 42.2 years with an equal number of males and females. More than half (55.2%) of the patients had right sided weakness (p =

0.025), with only one patient that had bifacial weakness. The HIV frequency was 34.5% (20/58) of which 11/20 (55%) were known HIV positive prior to Bell's diagnosis, and 9/20 (45%) were newly diagnosed HIV at the time of Bell's diagnosis. Known HIV positive patients were more likely to present with right sided weakness (10/11; 90.9%). The mean CD4 count at Bell's diagnosis did not show a statistically significant difference (p = 0.553) between the known HIV and newly diagnosed HIV group, namely 335 cells/μL for the former, and 243 cells/μL for the latter group. Among the HIV negative and newly diagnosed HIV positive patients, diabetes mellitus was the most common other associated co-morbidity.

Conclusions: In this cohort of patients in whom LMN facial weakness (Bell's palsy) was the presentation in all the patients, an HIV frequency of 34.5% was found. It can be the presenting problem in HIV or occur in the later stages of the disease. Right sided weakness was significantly more common in patients previously diagnosed with HIV and the mean CD4 count was > 200 cells/μL at presentation with Bell's in both HIV positive subgroups. Diabetes mellitus is a co-morbidity commonly associated with Bell's in HIV negative patients.

VI. ACKNOWLEDGEMENTS

I am especially grateful to Professor Girish Modi for his insight and guidance as my supervisor.

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x. NOMENCLATURE

AIDS	Acquired Immunodeficiency Syndrome
ANA	Antinuclear Antibody
ART	Antiretroviral Therapy
CD4	Cluster of Differentiation 4
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ENT	Ear, Nose and Throat
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HJH	Helen Joseph Hospital
HSV	Herpes Simplex Virus
LMN	Lower Motor Neuron
MRI	Magnetic Resonance Imaging
OPD	Outpatient Department
PLHIV	Persons Living with HIV
RPR	Rapid Plasma Reagin
SA	South Africa
SLE	Systemic Lupus Erythematosus
TPHA	Treponema Pallidum Haemagglutination
VL	Viral Load
WHO	World Health Organization

1 CHAPTER 1: PROTOCOL AND EXTENDED REVIEW OF THE LITERATURE

1.1 Introduction and extended review of literature

1.1.1 General information on idiopathic peripheral facial nerve palsy (Bell's palsy)

Bell's palsy (Bell's) is the most common disease of the facial nerve[1] accounting for 60 to 75% of facial nerve palsies[2] with an incidence of between 13 and 34 cases per 100 000 population.[3] There is no male or female predominance and can occur at any stage of life[4] but has a peak incidence between the second and fourth decades of life.[2] It is characterized by acute onset (usually unilateral) lower motor neuron (LMN) weakness of the facial nerve in the absence of other neurological deficits,[4] with the distinction between central or peripheral origin of the weakness being important as part of the initial evaluation.[5] Otalgia or postauricular pain, dysgeusia, sensory symptoms in the face and hyperacusis are often part of the symptomatology at the onset of Bell's and localizes to the intratemporal part of the facial nerve as the area of dysfunction.[1, 6] Patient age, severity (as quantified by the House-Brackmann scale), time from onset of symptoms to start of recovery, time from symptom onset to commencement of corticosteroid treatment, pain, dyslipidaemia, diabetes, hypertension and body weight are factors that are associated with the prognosis of BP.[7]

Eviston et al. pointed out that certain patterns of facial nerve palsy are important to recognize as they are associated with an underlying disease, and should hence not just be labelled as idiopathic facial paralysis.[4] These patterns are recurrent facial palsy (more suggestive of neoplasm), bilateral facial palsy (Guillain-Barré Syndrome and neoplasm),

facial palsy at birth and facial palsy syndromes (Ramsay-Hunt syndrome, Melkersson-Rosenthal syndrome and Heerfordt-Waldenström syndrome)[4] In an article by Donald H. Gilden, he summarized the different localizations and corresponding clinical features of facial nerve damage in table form (see **Table 1**), again indicating the importance of a thorough neurological examination in order to correctly localize the origin of the facial weakness.[5]

Table 1: *Clinical and anatomical features of facial nerve damage*

Site of Damage	Facial-Nerve Signs	Common Associated Features	Common Causes
Cortex, subcortical region	Contralateral central facial weakness; lacrimation, salivation, and taste intact	Contralateral hemiparesis and spasticity	Cortical or subcortical infarct
Pons	Ipsilateral peripheral facial weakness; lacrimation, salivation, and taste intact	Contralateral hemiparesis, sensory loss, ataxia, nystagmus, ipsilateral abducens palsy, ophthalmoparesis	Pontine infarction, glioma, multiple sclerosis
Cerebellopontine angle	Ipsilateral peripheral facial weakness; lacrimation, salivation, and taste usually intact	Tinnitus, facial numbness, ataxia, nystagmus	Acoustic or facial neuroma, meningioma, cholesteatoma, lymphoma, aneurysm, sarcoidosis
Facial nerve in internal auditory canal proximal to or involving geniculate ganglion	Ipsilateral peripheral facial weakness; lacrimation, salivation, and taste likely to be involved	Tinnitus, nystagmus, hearing loss	Bell's palsy, the Ramsay Hunt syndrome, acoustic or facial neuroma
Facial nerve distal to internal auditory canal and geniculate ganglion	Ipsilateral peripheral facial weakness; lacrimation intact but salivation and taste impaired	Tinnitus, nystagmus, hearing loss	Bell's palsy, temporal-bone fracture, cholesteatoma or glomus tumor, middle-ear infection
Facial nerve in stylomastoid foramen	Ipsilateral peripheral facial weakness; lacrimation, salivation, and taste intact	Head injury, parotid mass	Head injury, parotid tumor

Reprinted from "Bell's Palsy", Gilden DH, 2004, New England Journal of Medicine, 351:1323-31.

According to Zandian et al.[8] the term "Bell's palsy" is synonymous with "idiopathic peripheral facial paralysis." This is also stated by D.G. James in his article titled "All that palsies are not Bell's."[9] According to Adour, Bell and Hilsinger, peripheral facial palsy is a syndrome of many causes with herpes simplex virus (HSV) activation being the likely cause in most cases. They also point out that most patients with peripheral facial palsy is

labelled as having Bell's, as there is no established or widely available method of confirming HSV as the cause.[10] The presence of HSV-1 in intratemporal facial nerve endoneural fluid further supports the theory that Bell's is caused by reactivation of HSV-1,[11] but according to Zandian et al., the aetiology of Bell's is unknown.[8] Gilden et al. points out that in two thirds of all patients with peripheral facial weakness it is idiopathic and that the remaining one third is caused by trauma, diabetes mellitus, hypertension, eclampsia, Ramsay Hunt syndrome (facial weakness with zoster oticus with varicella–zoster virus infection), Lyme disease, sarcoidosis, Sjögren's syndrome, parotid gland tumours and amyloidosis.[12] In an article published in 2018 in "Medical Clinics of North America" Owusu et al. divided the causes of facial paralysis into idiopathic (Bell's palsy), infectious, neoplastic and trauma.[13]

The exact pathophysiology of non-traumatic isolated facial nerve palsy is unknown. Greco et al. refers to a viral hypothesis and an immunological hypothesis as postulated pathophysiological processes causing Bell's.[2] The epidemiology,[14] flu-like symptoms prior to the onset of weakness (Greco et al.[2] quoted Kynvett et al.) and gadolinium enhancement on MRI imaging of the geniculate ganglion during the acute phase of the illness[15] are the features of Bell's that substantiate the hypothesis of a viral mechanism or cause. Viruses associated with Bell's are Epstein-Barr,[16] cytomegalovirus,[17] mumps,[18] rubella[19] and human immunodeficiency virus (HIV).[20] According to Morgan et al.[21] there is however no unequivocal association between Bell's and the above-mentioned viral pathogens.

The other pathophysiological process suggested is an autoimmune mechanism[22,23,24] involving both the humoral and cell-mediated components of the acquired immune

system.[25] It may also be a combination of both of the above-mentioned mechanisms (viral & immune) with a viral pathogen leading to an autoimmune response against a component of the myelin surrounding the axons in peripheral nerves, with the end result being demyelination clinically evident as LMN weakness.[26] The improvement of symptoms and signs in the majority of patients with Bell's is also supporting the demyelination hypothesis with reference to the fact that improvement is unlikely to occur if the nerve itself had been damaged.[2] Yet another possible mechanism is swelling and subsequent compression of the nerve with the swelling occurring secondary to a viral infection.[27,28] As evident in the description of the possible pathophysiological processes thus far, a viral aetiology is central to or part of most hypotheses.

1.1.2 HIV and the nervous system

HIV is associated with many nervous system disorders or complications involving both the central and peripheral nervous system resulting in significant morbidity and mortality.[29] HIV invasion into the nervous system occurs early in the infection (neuro-invasive as described by Manji and Miller) and is neurovirulent leading to dementia, myelopathy, neuropathy and myopathy.[30] Opportunistic infections, most notably tuberculosis, cerebral toxoplasmosis and cryptococcal meningitis, and HIV-associated malignancy, including primary and secondary central nervous system lymphoma, are other common diseases associated with HIV.[30] In the late highly active antiretroviral therapy (HAART) era, opportunistic infections remain the most common cause of death in the HIV positive population.[31]

Seroconversion can present as aseptic meningitis, facial palsy, Guillain-Barré syndrome (GBS) and transverse myelitis.[32] Centner, Bateman and Heckmann also indicate that HIV invades both the central and peripheral nervous system soon after infection and that cranial mononeuropathies are frequently encountered in HIV, with the facial nerve being involved most of the time. It can be unilateral or bilateral and usually occurs as a peri-inflammatory (within six weeks before seroconversion) or postinflammatory palsy (in the first weeks of seroconversion) around the time of primary HIV infection. They indicate that recovery is similar to HIV negative patients with Bell's.[33] In the article titled "Neurological manifestations in HIV infection in Nigerians", conducted in 2003, eight patients (3.9% of the study population) had lower motor neuron facial weakness, with this being the presenting feature of HIV in all of them.[29] In their 2018 article, Dong and Jung et al. evaluated the neutrophil to lymphocyte ratio in patients with delayed recovery from Bell's, but did however not make any reference to a possible relationship between HIV and Bell's with regards to the neutrophil to lymphocyte ratio, nor the prognosis of the latter in this regard or with these parameters.[7]

Miszkiel and Miller examined the MRI appearance of the facial nerve in an HIV positive patient with acute facial nerve palsy. They noted that the enhancement pattern in their report is the same as that observed in Bell's. They explain that HIV is a neurotropic virus and upon entry into the facial nerve and geniculate ganglion, it causes an inflammatory reaction resulting in endoneural swelling and subsequent compression of the nerve, resulting in the MRI findings as noted.[34] Wichmann et al. concluded that the enhancement observed on MRI in patients with idiopathic, herpetic and HIV-associated peripheral facial palsy is the result of blood-peripheral nerve barrier breakdown and also epi- and perineural

venous plexuses congestion.[35] It was mentioned above that there are certain patterns of facial nerve weakness that should be sought as it is associated with other localizations and underlying pathology. Serano et al. described two patients with bilateral Bell's in acute HIV Type 1 infection.[36] Morales et al. had a case report of a patient initially presenting as suspected left Bell's, but was later found to have PML-IRIS, with a non-enhancing lesion in the left facial colliculus on MRI brain, accounting for the ipsilateral LMN facial weakness and confirming the central localization of the deficit.[37] This again highlighting the importance of a thorough evaluation and confirmation of localization, especially in the context of worsening and/or the subsequent development of other deficits, as was the case in the report noted above.

The CD4 cell count is a biomarker for the assessment of immunocompetence in HIV infected individuals, but a normal CD4 count does however not always imply normal immune function[33] and neurological complications or manifestations are seen in all stages of HIV.[30] The CDC correlated the WHO clinical stages 1 to 3 of HIV with the CD4 count. Stage 1 is defined as CD4 $\geq$ 500 cells/μL, stage 2 has a CD4 of 200-499 cells/μL and stage 3 a CD4 < 200 cells/μL (CD4 < 200 being AIDS defining).[38]

Table 2: *CD4-related presentation*

Seroconversion and/or CD4 >500	CD4 >200 – <500	CD4 <200
Aseptic meningitis	TB meningitis	HIV-associated dementia
Meningoencephalitis	Guillain-Barré syndrome	TB meningitis
Bell's palsy	DSPN	Cryptococcal meningitis
Guillain-Barré syndrome	Polymyositis	Toxoplasmosis
Brachial neuritis	MND	PML
Transverse myelitis		Primary CNS lymphoma
		Nocardia brain abscess
		DSPN
		Vacuolar myelopathy
		CMV encephalitis
		Ischaemic CVA
		Herpes encephalitis
		CMV radiculopathy

CMV = cytomegalovirus; CNS = central nervous system; CVA= cerebrovascular accident; DSPN = distal symmetrical polyneuropathy; MND = mild neurocognitive disorder; PML = progressive multiofocal leukoencephalopathy; TB= tuberculosis.

Reprinted from "Neurological complications in HIV", Hogan C, Wilkins E, 2011, Clinical Medicine, Vol. 11, 571-5.

As stated above, neurological diseases occur during all stages of HIV infection, but there is also a correlation between certain neurological (and other systemic) diseases and the CD4 count.[32,39] (See **Table 2**). Modi et al. studied the prevalence of neurological illnesses in a clade C HIV endemic area and emphasized the relevance of the CD4 categorization and its association with different neurological illnesses.[40] Another important biological maker that correlates with the presence of neurological illnesses in HIV positive patients is the CSF viral load (VL). Morandini et al. however points out that the plasma HIV RNA level does not correlate with the CSF VL.[41] According to Price and Spudich, in chronic HIV-1 infection there can be a divergence of or difference between the HIV populations in the plasma and CSF.[42] They also mention that functional compartmentalization has also been

associated with drug resistance, but conclude that despite this viral escape or compartmentalization phenomenon, antiretroviral therapy (ART) still has a significant positive impact on central nervous system diseases as a result of HIV infection, specifically with regards to opportunistic infections and HIV-associated dementia. In their article there were no references made with regards to ART and improvement of HIV-associated neurological manifestations in the peripheral nervous system. No studies could however be found linking the compartmentalization of HIV in CSF and cranial mononeuropathies. Interestingly, Kohler and Burkhard et al. reported seven cases of isolated peripheral facial palsy that occurred in different stages of HIV infection and found that the cerebrospinal fluid was abnormal in all seven patients.[43]

Despite the advent of ART, neurological disease still accounts for 2-3% of the presenting features of HIV and, although there is an improvement in the incidence of neurological disease associated with HIV, the spectrum of diseases has stayed unchanged.[32] No studies were found that specifically evaluated the effect of early ART initiation on the prevalence of BP in HIV positive patients, whether they have been on treatment for a long time, or after initiation of ART when Bell's was the presenting problem.

1.1.3 HIV in South Africa

According to the 2021 mid-year population estimates released by "Statistics South Africa," the number of persons living with HIV (PLHIV) in SA increased from about 3.8 million in 2002 to 8.2 million in 2021, accounting for an estimated 13.7% of the total population living with HIV.[44] The prevalence is highest among women of childbearing age (indicated as 15-

49 years in the report) with approximately one fifth of women in this age group being HIV positive.[44] Since 01 April 2013 the eligibility criteria for the commencement of antiretrovirals (ARVs) in HIV positive patients in South Africa changed and allowed all newly diagnosed HIV positive patients, pregnant women and breastfeeding mothers to be initiated on the fixed-dose combination (FDC), provided there are no contra-indications.[45] FDC is a combination of tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV). By the end of June 2018, 4.5 million people in South Africa were on antiretroviral therapy and according to "UNAIDS" estimates this led to a reduction in the AIDS-related (acquired immunodeficiency syndrome) deaths, with a decrease from 200 000 deaths in 2010 to 110 000 in 2017.[46]

As alluded to above, ART has had a positive impact on the morbidity and mortality of neurological illnesses in the HIV population.[32] Most studies in this regard comment on the reduction in opportunistic infections (that is still highly prevalent and the leading cause of death)[47] but not the effect on morbidity of peripheral nervous system involvement in HIV, specifically facial mononeuropathy.

1.1.4 Bell's palsy and HIV

According to Centner, Bateman and Heckmann, HIV positive patients frequently develop cranial mononeuropathies, with facial nerve involvement being the most common.[33] However, in the seventh edition of "Cummings otolaryngology," published in 2021, they note that the more common occurrence of idiopathic facial nerve paralysis in HIV positive patients has not been substantiated thus far.[48]

In the series by Riancho et al. they observed that the CD4 varied widely at the time of presentation of Bell's, between 27 and 895 cells/μL, with a median of 232 and stated that Bell's can occur at any stage of the disease,[49] whereas Hogan et al. reported Bell's as a CD4-related presentation occurring at seroconversion and/or at a CD4 of > 500.[32] The HIV VL also varied widely in HIV positive patients presenting with facial weakness in the same study noted above by Riancho et al.[49] No literature correlating the HIV VL with Bell's presentation could be found. Zhao et al. analyzed 372 consecutive patients with Bell's and found that the peak age of presentation was in the fourth decade of life[50]. A South African study by Magazi et al. however found a significant association between Bell's and age <30 years, also noting that HIV positivity and seasonality are independent risk factors for Bell's, but an association between a younger age and HIV status was not mentioned.[51] Another African study, conducted in Nigeria, also found that most of their patients were in their third decade of life.[52]

1.2 Conclusion and motivation for the study

Literature confirms the association between HIV and Bell's. There are however differences in the demographics and some clinical characteristics in this regard with a paucity of recent studies in HIV-endemic areas in the post-ARV era focussing on HIV in Bell's palsy. This study aims to ascertain this association between HIV and Bell's and elaborate on the demographic characteristics as well as some clinical characteristics of patients that present with Bell's to the neurology units in Johannesburg, South Africa.

1.3 Study Objectives

1. Describe the sociodemographic characteristics of patients with Bell's that presented with or followed-up for Bell's at the following hospitals and clinics:
    - Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)
        - Neurology Outpatients Department
        - Otorhinolaryngology (Ear, Nose and Throat) Outpatient Department
    - Chris Hani Baragwanath Academic Hospital (CHBAH)
        - Neurology Outpatients Department
        - Otorhinolaryngology (Ear, Nose and Throat) Outpatient Department
    - Helen Joseph Hospital (HJH)
        - Neurology Outpatients Department
        - Otorhinolaryngology (Ear, Nose and Throat) Outpatient Department
        - Polyclinic
2. Determine the frequency of HIV in patients with newly diagnosed Bell's at the tertiary centres as indicated above.
3. Determine the mean CD4 and VL of the patients in the HIV positive subgroup.

1.4 Methodology

1.4.1 Study Design

A retrospective-prospective observational and descriptive study with the data spanning a three-year period, from January 2019 to the end of November 2021.

1.4.2 Setting

The data will be obtained at the following departments and clinics:

- Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)
    - Neurology Outpatients Department
    - Otorhinolaryngology (Ear, Nose and Throat) Outpatient Department
- Chris Hani Baragwanath Academic Hospital (CHBAH)
    - Neurology Outpatients Department
    - Otorhinolaryngology (Ear, Nose and Throat) Outpatient Department
- Helen Joseph Hospital (HJH)
    - Neurology Outpatients Department
    - Otorhinolaryngology (Ear, Nose and Throat) Outpatient Department
    - Polyclinic

1.4.3 Methods of assessment or measurement

A data capturing sheet will be used to obtain the data for each patient (see appendices). These data capturing sheets will be completed by myself or the doctor that first evaluated the patient at the respective departments. All patients 18 years and older that followed-up for or presented with non-traumatic unilateral or bilateral lower motor neuron facial weakness (Bell's palsy) will be included. Informed consent will be obtained from each patient, for both the use of the clinical information as indicated on the data capturing sheet, as well as HIV testing if the patient's HIV status is unknown. All patients will stay anonymous during the course of the study.

1.4.4 Eligibility Criteria

All patients 18 years and older with isolated unilateral or bilateral LMN facial weakness in the absence of other neurological deficits or facial weakness of central origin at the time of diagnosis of Bell's.

1.4.5 Exclusion Criteria

- Patients younger than 18 years of age.
- Traumatic or structural cause identified as the aetiology of the facial palsy.
- Central nervous system (brain and brainstem) pathology identified.

1.5 Data collection, management, and statistical analysis

1.5.1 Data collection

An informed consent form and data sheet will be completed for all eligible patients and a study number will be allocated to each patient included in the study. The information that will be captured for each patient is stipulated below. If a patient's HIV status, CD4 or VL is unknown (if the patient is HIV positive), these blood tests will be done with the necessary consent for HIV testing (see appendices). In addition, the HbA1c, TPHA and ANA will be done if a patient is not known to have diabetes mellitus, syphilis, or an auto-immune disease. These laboratory investigations are part of the routine workup of all patients that present with facial weakness and will hence not imply extra unnecessary costs only for the sake of this study.

Information required for each patient and indicated on the data capturing sheet:

- Demographic information
    - Age
    - Gender
- Study number
- Date of diagnosis of Bell's Palsy
- Side of face involved
- HIV status (All patients)
    - If HIV positive:
        - Date of diagnosis of HIV
        - CD4 at the time of diagnosis of HIV
        - VL at the time of diagnosis of HIV
        - CD4 at the time of diagnosis of Bell's palsy
        - VL at the time of diagnosis of Bell's palsy
        - If on treatment:
            - ARV regimen
            - Time of commencement
- HbA1c
- TPHA and RPR tests
- ANA test

1.5.2 Power calculation

Due to the paucity of recent research and literature regarding prevalence studies of HIV in Bell's, a convenient sampling method will be used. A power calculation will be done with "Stata" software using a 5% level of significance to detect the effect.

1.5.3 Statistical methodology and analysis

1.5.3.1 Objective 1:

The demographic variables that will be evaluated are age and gender. Age is a continuous numerical variable for which a mean and standard deviation will be determined, provided the data is normally distributed. If the data is not normally distributed, the median and interquartile range will be determined. Gender is a nominal categorical variable for which the frequency and percentage will be determined for each.

1.5.3.2 Objective 2:

The frequency of HIV in the study population will be determined by means of frequencies and percentages using tabulation.

1.5.3.3 Objective 3:

The CD4 and VL are continuous variables and as described at objective 1, the mean and standard deviation will be determined for normally distributed data, whereas the median and interquartile range will be used if the data is not normally distributed.

1.6 Ethics

The protocol will be submitted to the Human Research Ethical Committee of the University of Witwatersrand for evaluation and approval. All patients will stay anonymous and only the relevant clinical information as indicated on the data capturing sheet will be used. Informed consent will be obtained for each patient.

1.7 Funding

All costs incurred during this research project will be paid for personally and no costs will be imposed on the hospital or patients and no extra funding will be obtained.

1.8 Timing

The study will commence once ethics approval has been received. Patients will be recruited and enrolled in the study spanning a period of three years. Data collection will occur concurrently after which data analysis and final write-up will commence. The Gantt chart in **Table 3** shows the timeline for the study.

***Table 3**: Gantt chart showing the timeline of the study*

	Mar ' 19 – Aug ' 19	Sep – Oct 2019	Nov ' 19 – March ' 20	Apr ' 20 – Nov ' 21	Dec ' 21 – May ' 22	Jun – Sep ' 22
Protocol development						
Protocol assessment						
Ethics application						
Data collection						
Data analysis						
Writing up research report						

1.9 Limitations

- Time period planned to obtain the data.
- Risk of getting patients with unknown HIV status at the time of diagnosis of Bell's.
- Availability of all the information indicated on the data sheet, specifically with regards to the CD4 and VL for HIV positive patients.
- This is a hospital-based study and can hence miss patients that were diagnosed and followed-up at primary care level. Thus, the number of patients presenting at tertiary hospitals may not be sufficient.

1.10 References

See chapter 2.9 for full list of references.

2 CHAPTER 2: PROPOSED MANUSCRIPT

THE FREQUENCY OF HIV IN PATIENTS WITH NEWLY DIAGNOSED BELL'S PALSY AT A TERTIARY CENTRE

2.1 Background on Bell's palsy

2.1.1 Epidemiology

Bell's palsy (Bell's), named after the Scottish anatomist, Sir Charles Bell,[53] is an idiopathic isolated lower motor neuron facial weakness of acute onset, in the absence of corticospinal tract signs[51] and has an incidence of between 13 and 34 cases per 100 000 population.[3] It occurs with equal frequency in both males and females, with a maximum incidence with regards to age between 15 and 45 years.[54] Interestingly, in the South African context, Magazi et al. recently found a peak age of less than 30 years, a finding that is at variance with studies conducted in Europe and Asia that reportedly have a peak in Bell's in the fourth and fifth decade.[51] Other studies conducted on the African continent also reported a younger age group in the context of HIV seropositivity.[55, 56, 57] The seasonality of Bell's has also been a topic of discussion and a component of research with different studies reporting different seasonal patterns[51] or no associations with climate at all,[58] with a recent South African study being the first to report a seasonal cyclical occurrence of BP.[51]

2.1.2 Clinical picture, severity, and associated aetiologies

Bell's usually presents as unilateral, LMN facial weakness that reaches maximal disability in the first 48 – 72 hours[4] in the absence of other neurological abnormalities.[59] The severity of the facial weakness can be graded using the House-Brackmann[60] or Sunnybrook[61] score. As is the case with any neurological problem or deficit, the exact clinical description thereof and subsequent localization is of the utmost importance, with facial weakness not being an exception. Fuller and Morgan aptly highlight this principle with reference to facial weakness in their article, advocating that Bell's palsy should rather be referred to as "Bell's palsy syndrome," hereby urging the clinician not to stop at the assessment of LMN facial

weakness, but to entertain a differential diagnosis and work up appropriately.[62] Eviston et al. refer in their article published in "The Journal of Neurology, Neurosurgery and Psychiatry" to four patterns of facial palsy, namely recurrent, bilateral, congenital and syndromic, each with associated aetiologies.[4] In the context of this report with the emphasis being on HIV, it is important to mention bilateral facial weakness and the necessity to evaluate for other associated neurological deficits or signs, as bifacial weakness can be caused by basal meningitis, Guillain-Barré syndrome and myasthenia gravis.[62] Despite it being an atypical presentation, isolated bilateral facial weakness can develop at seroconversion in HIV positive patients,[36] with Serrano et al. reporting that all cases of HIV-associated bifacial weakness in their literature review occurred in the context of aseptic meningitis.[36] Other red flag signs that should prompt the clinician to evaluate for an alternative diagnosis are vestibulocochlear abnormalities other than hyperacusis, severe pain, other systemic abnormalities, history of cancer, prior tick bite and rash in the external auditory meatus.[62] Furthermore, with Bell's there can be associated symptoms accompanying the facial weakness which includes postauricular pain, dysgeusia, hyperacusis and a subjective change in facial sensation.[4, 62]

There is a higher incidence of Bell's in diabetes mellitus, hypertension, pregnancy, after upper respiratory viral infections and in patients who are immunocompromised.[54] Gilden et al. points out that in two thirds of all patients with peripheral facial weakness it is idiopathic and that the remaining one third is caused by trauma, diabetes mellitus, hypertension, eclampsia, Ramsay Hunt syndrome (facial weakness with zoster oticus with varicella–zoster virus infection), Lyme disease, sarcoidosis, Sjögren's syndrome, parotid gland tumours and amyloidosis.[12] As alluded to earlier, Bell's is associated with HIV

infection[51, 52] with facial nerve involvement being the most common cranial neuropathy in HIV.[63] The facial weakness can be unilateral or bilateral and can occur at any time during the course of the HIV infection,[52,63] with Belec et al. concluding that the assessment of HIV-related Bell's is the most plausible diagnosis in the early stages of HIV, while in the late stages there can be a variety of other causes.[64] With regards to co-morbidities in the setting of an HIV-endemic area, it is worth mentioning that Riancho et al. documented hepatitis C co-infection in 75% of their study population, consisting only of HIV positive patients with Bell's.

In general, younger patients with Bell's have a better prognosis.[54] The prognosis of facial palsy in early HIV infection corresponds to that in the general population according to Riancho et al.[49] while in a Nigerian study by Komolafe et al. patients with HIV-related Bell's appeared to have a more severe deficit.[52] Similarly, Milogo et al. also reported that the facial weakness in HIV positive patients were more severe and had a longer duration of symptoms as compared to the HIV negative patients.[55] Most of the patients in the series by Sathirapanya et al. had a satisfactory recovery regardless of the treatment, a finding corroborated by their literature review.[63] The presentation in early HIV infection seems to be a good prognostic factor with a subsequent shorter duration of weakness.[65] Diallo et al. reported that in their study population with an HIV prevalence of 42.86%, 62.5% of their patients had complete recovery.[56] Recurrent Bell's in HIV positive patients, in the absence of other aetiologies, has also been documented before,[57] whereas Komolafe et al. did not find a statistically significant relationship between HIV positivity and recurrent facial weakness.[52] The latter authors indicated that diabetes mellitus, underlying malignancy,

sarcoidosis and Melkersson-Rosenthal syndrome could predispose to recurrent facial weakness.[52]

2.1.3 Pathophysiology

The exact pathophysiology of non-traumatic isolated facial nerve palsy is unknown. Greco et al. refers to a viral hypothesis and an immunological hypothesis as postulated pathophysiological processes causing Bell's.[2] The epidemiology,[14] flu-like symptoms prior to the onset of weakness (Greco et al.[2] quoted Kynvett et al.) and gadolinium enhancement on MRI imaging of the geniculate ganglion during the acute phase of the illness[15] are the features of Bell's that substantiate the hypothesis of a viral mechanism or cause. Viruses associated with Bell's are Epstein-Barr,[16] cytomegalovirus,[17] mumps,[18] rubella[19] and human immunodeficiency virus (HIV).[20] According to Morgan et al.[21] there is however no unequivocal association with Bell's and the above-mentioned viral pathogens.

The other pathophysiological process suggested is an autoimmune mechanism[22,23,24] involving both the humoral and cell-mediated components of the acquired immune system.[25] It may also be a combination of both of the above-mentioned mechanisms (viral & immune) with a viral pathogen leading to an autoimmune response against a component of the myelin surrounding the axons in peripheral nerves, with the end result being demyelination clinically evident as LMN weakness.[26] This is also the case in HIV-associated facial neuropathy, where the neuropathy is the consequence of immunologically-mediated neural inflammation in early HIV infection.[63] The improvement of symptoms and signs in the majority of patients with Bell's is also supporting the

demyelination hypothesis with reference to the fact that improvement is unlikely to occur if the nerve itself had been damaged.[2] Yet another possible mechanism is swelling and subsequent compression of the nerve with the swelling occurring secondary to a viral infection[27,28] with the extra-axial segment being most commonly involved in early HIV infection.[52]

As evident in the description of the possible pathophysiological processes thus far, a viral aetiology is central to or part of most hypotheses. Specifically with regards to HIV, in addition to the processes noted above, oxidative stress may also play a role, as HIV is associated with this biochemical process in both the central peripheral nervous system.[66, 67] An immunological hyperreaction to the HIV viraemia signifies that the host's immunity is still competent, hence the occurrence of Bell's in the early stages of the disease. [63]

2.1.4 Treatment

Gilden quoted Adour et al. where he noted that 71% of untreated patients recover completely and 84% have near normal residual function.[5] Medical treatment with oral prednisone is recommended in all cases with the addition of antiviral treatment in severe cases.[68] Specifically with regards to HIV, a beneficial effect of ART, specifically with regards to the effect on facial weakness, has not been confirmed thus far, but as there is a suspected immunologically mediated inflammatory process involved, prednisone is still indicated in this setting as well.[69] Despite the advent of ART, neurological disease still accounts for 2-3% of the presenting features of HIV and, although there is an improvement in the incidence of neurological disease associated with HIV, the spectrum of diseases has

stayed unchanged.[32] No studies could however be found that specifically evaluated the effect of early ARV initiation on the prevalence of Bell's in HIV positive patients, whether they have been on treatment for a long time, or after initiation of ARVs when Bell's was the presenting problem.

2.1.5 Additional aspects related to HIV-associated Bell's palsy

2.1.5.1 Frequency of HIV in Bell's in literature review

There seems to be a variation in the frequency of HIV in Bell's, with all the studies in the literature review, spanning a period of more than 25 years, documenting a frequency of ≥ 25%: Balogou et al. in Togo during the early 1990s reported an HIV seroprevalence of 52%,[57] while Amayo et al. (1991) reported it to be 25%.[70] Millogo et al. (2000) in Burkina Faso reported a frequency of HIV of just over 55%,[55] while Casanova-Sotolongo et al. (2001) found that 89.1% of their patients had HIV.[71] Diallo et al. (2017) documented an HIV prevalence of 42.86% over a study period of 12 months in patients that presented with peripheral facial palsy.[56]

2.1.5.2 CD4 and VL

The CD4 cell count is a biomarker for the assessment of immunocompetence in HIV infected individuals, but a normal CD4 count does however not always imply normal immune function[33] and neurological complications or manifestations are seen in all stages of HIV.[30] The CDC correlated the WHO clinical stages 1 to 3 of HIV with the CD4 count. Stage 1 is defined as CD4 ≥ 500 cells/μL, stage 2 has a CD4 of 200-499 cells/μL and stage 3 a CD4 < 200 cells/μL (CD4 < 200 being AIDS defining).[38]

Neurological diseases occur during all stages of HIV infection, but there is also a correlation between certain neurological (and other systemic) diseases and the CD4 count.[32,39] Modi et al. studied the prevalence of neurological illnesses in a clade C HIV endemic area and emphasized the relevance of the CD4 categorization and its association with different neurological illnesses.[40]

Another important biological maker that correlates with the presence of neurological illnesses in HIV positive patients is the CSF VL. Morandini et al. however points out that the plasma HIV RNA level does not correlate with the CSF VL.[41] According to Price and Spudich, in chronic HIV-1 infection there can be a divergence of or difference between the HIV populations in the plasma and CSF.[42] They also mention that functional compartmentalization has also been associated with drug resistance, but conclude that despite this viral escape or compartmentalization phenomenon, ART still has a significant positive impact on central nervous system diseases as a result of HIV infection, specifically with regards to opportunistic infections and HIV-associated dementia. In their article there were no references made with regards to ART and improvement of HIV-associated neurological manifestations in the peripheral nervous system. No studies could however be found linking the compartmentalization of HIV in CSF and cranial mononeuropathies. Interestingly, Kohler and Burkhard et al. reported seven cases of isolated peripheral facial palsy that occurred in different stages of HIV infection and found that the cerebrospinal fluid was abnormal in all seven patients.[43] It has been mentioned above that Serrano et al. reported that all cases of isolated bifacial weakness they found in their literature review were associated with aseptic meningitis.[36]

Most studies that do include and report on serological markers, predominantly refer to the CD4, with a paucity of literature specifically focussing on the VL in the context of HIV-associated Bell's. In the case series by Sathirapanya et al. they found a mean CD4 of 274 cells/μL but did not comment on the VL of these patients.[63] In the study by Diallo et al. the CD4 levels ranged between 175 and 400 cells/μL with no comments on the VL of the seropositive patients.[56]

The narrative on Bell's and HIV as well as the significance of the CD4, VL and ART regimes is far from complete nor comprehensive with a lot potential areas of interest for future research, especially in light of new drugs and treatment regimes.

2.2 Aims

1. Describe the sociodemographic characteristics of patients with Bell's that presented with or followed-up for Bell's at the following hospitals and clinics:
    - Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)
        - Neurology Outpatients Department
        - Otorhinolaryngology (Ear, Nose and Throat) Outpatient Department
    - Chris Hani Baragwanath Academic Hospital (CHBAH)
        - Neurology Outpatients Department
        - Otorhinolaryngology (Ear, Nose and Throat) Outpatient Department
    - Helen Joseph Hospital (HJH)
        - Neurology Outpatients Department
        - Otorhinolaryngology (Ear, Nose and Throat) Outpatient Department

- Polyclinic

2. Determine the frequency of HIV in patients with newly diagnosed Bell's at the tertiary centres as indicated above.
3. Determine the mean CD4 and VL of the patients in the HIV positive subgroup.

2.3 Methods

2.3.1 Design and setting

This is a retrospective-prospective observational and descriptive study. Patients who presented with Bell's palsy from January 2019 to March 2020 and followed-up at the clinics (mentioned above) were retrospectively added (where the date of HIV test and other blood results were available at time of Bell's diagnosis), after which patients from April 2020 to November 2021 were prospectively recruited. The initial data collection period was planned to be one year, but due to the small sample size and COVID-19 pandemic, the study period for data collection was extended. Data was collected at the hospitals, departments and clinics noted above.

2.3.2 Participants

All patients 18 years and older with newly diagnosed non-traumatic LMN facial weakness with no other signs localizing to the brainstem (e.g. corticospinal tract signs) that were referred to or followed-up sequentially at the Neurology clinics at CMJAH, CHBAH and HJH as well as HJH polyclinic were included in the study.

Informed consent for both participation in the study and the use of the HIV status were obtained for each patient. The data was subsequently captured during prospective patient interviews using a data capturing sheet for each patient (see appendices for informed consent forms and data capturing sheets.)

Information required for each patient and indicated on the data capturing sheet:

- Demographic information
    - Age
    - Gender
- Study number
- Date of diagnosis of Bell's Palsy
- Side of face involved
- HIV status (All patients)
    - If HIV positive:
        - Date of diagnosis of HIV
        - CD4 at the time of diagnosis of HIV
        - VL at the time of diagnosis of HIV
        - CD4 at the time of diagnosis of Bell's palsy
        - VL at the time of diagnosis of Bell's palsy
        - If on treatment:
            - ARV regimen
            - Time of commencement
- HbA1c
- TPHA and RPR tests

- ANA test

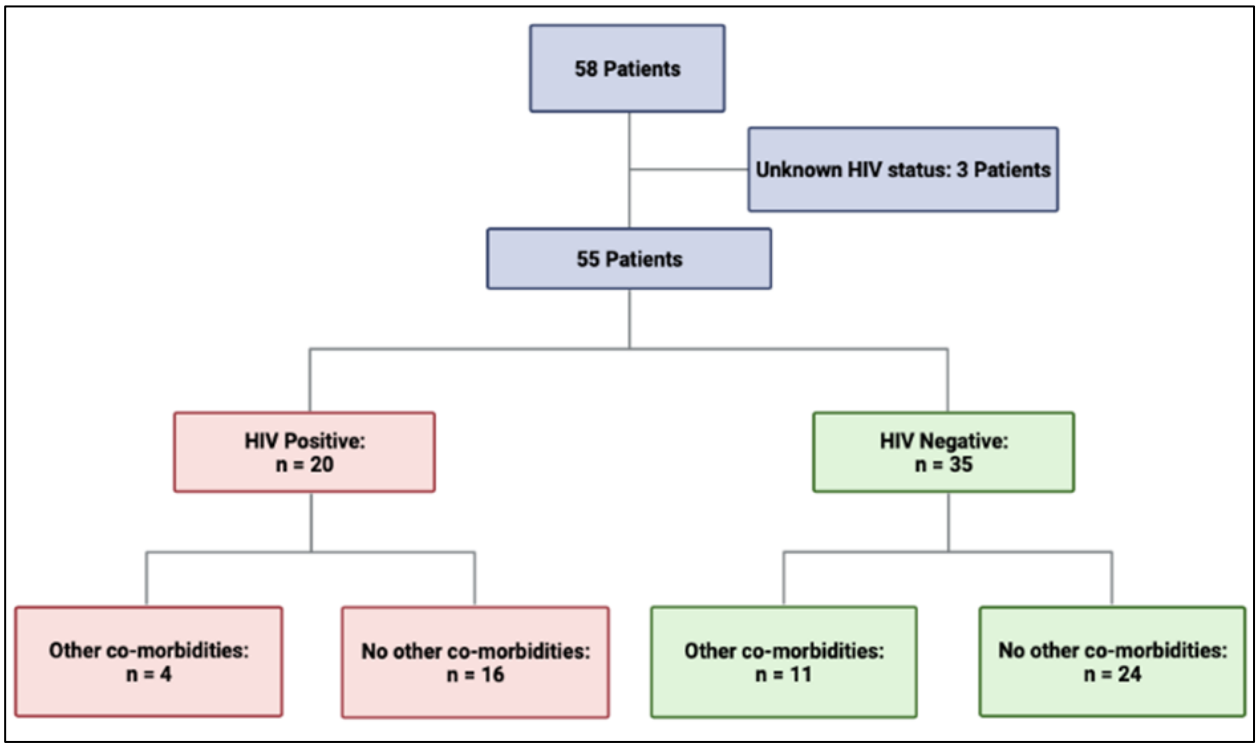
2.4 Statistical analysis

Data was captured in an “Excel” spreadsheet and then exported to “Stata 14.2” for analysis. Enrolled and captured patients were described using medians and interquartile range for continuous variables as well as frequencies and percentages for categorical variables. Descriptive statistics was also used to determine the frequency of HIV among patients with Bell’s palsy and median CD4 counts and viral loads among HIV positive patients. For categorical data, the X2 test was used to test the hypotheses that there were statistically significant differences in demographic or clinical characteristics of patients by HIV status. Where there were small numbers of patients in the different categories of the variables, the Fischer’s exact test was used. For continuous variables, the t-test was used for data that was normally distributed while Wilcoxon rank sum test or the K-test for equality of medians was used for data that was not normally distributed.

2.5 Results

Between 01 January 2019 and 30 November 2021, sixty (60) patients were enrolled and had data collection sheets completed. **Figure 1** provides a visual representation and breakdown of the number of patients categorized based on HIV status and co-morbidities. Of the 60 enrolled, two were ineligible for inclusion in the analysis because of the age less than 18 years. **Table 4** presents the demographic and clinical characteristics of the 58 patients included in the analysis.

Figure 1: *Diagram indicating breakdown of study population with regards to HIV status and other co-morbidities*



The mean age of the study population was 42.2 years (SD 13.5) with an equal number of males and females (29). Almost half of the patients were seen in 2021 (46%) with autumn (defined as the period March to May) as the season during which the highest number of patients were diagnosed with BP in this cohort (34.5%), followed by summer and equal numbers of patients (12%) during winter and spring.

Table 4: *Demographic and clinical characteristics of patients with Bell's palsy 2019 – 2021 (n=58)*

Variable	n(%)
Age in years (median, IQR)	40 (32- 51)*
Age in years (mean, SD)	42.2 (13.5)**
Gender	
Female	29 (50.0)
Male	29 (50.0)
Year of diagnosis	
2019	16 (27.6)
2020	15 (25.9)
2021	27 (46.6)
Season of diagnosis	
Summer (December – February)	14 (24.1)
Autumn (March – May)	20 (34.5)
Winter (June – August)	12 (20.7)
Spring (September – November)	12 (20.7)
Side of face affected	
Left	23 (39.7)
Right	32 (55.2)
Bilateral	1 (1.7)
Side unknown	2 (3.5)
HIV status at diagnosis	
HIV negative	35 (60.3)
HIV positive, known	11 (19.0)
HIV positive, newly diagnosed	9 (15.5)
HIV status unknown	3 (5.2)
One or more co-morbidities	15 (25.9)
Diabetes mellitus (n=15)	12 (80)
HbA1c levels	5.9 (5.3 - 6.6)*
Syphilis (n=15)	2 (13.3)
TPHA positive	2 (13.3)
RPR positive	1 (6.7)
Autoimmune conditions (n=15)	3 (21.4)
Other (n=15)	1 (0.1)

**Median and interquartile range; **Mean and standard deviation; IQR = interquartile range; SD = standard deviation*

More than half of the patients (55.2%) had right sided weakness, with only one patient that had bilateral facial palsy. The latter patient was also newly diagnosed HIV positive. HIV positivity was 34.5% (20/58) of which 11/20 (55%) were known HIV positive while 9/20 (45%) were newly diagnosed. Among the HIV positive subgroup, 8/20 (40%) were ART naïve at Bell's diagnosis while 9/20 (45%) were on ART and 3/20 (15%) did not have information on ART documented.

Of the 58 included, 15 (25.9%) patients had one or more other co-morbidities (apart from HIV), 11 of whom were HIV negative and four HIV positive. Three patients had more than one co-morbidity. Diabetes mellitus was the most common co-morbidity with a frequency of 20.7% (12/58), while representing 80% (12/15) of the patients with co-morbidities, most of whom (10/12) were also HIV negative. Two patients were TPHA positive, with only one having a positive RPR as well, along with being newly diagnosed HIV. Three patients had a positive ANA, with only one patient being confirmed to have systemic lupus erythematosus (SLE). One female was also found to be pregnant.

Table 5 compares characteristics of patients according to their HIV status, with HIV positive status categorized into newly diagnosed or known HIV. The three groups were similar with respect to age, gender distribution and year of diagnosis, however, most HIV negative individuals presented in the summer and autumn (74.3%) compared to newly diagnosed HIV positives who presented in winter and spring (77.7%) and known HIV positives who presented in autumn and spring (67.7%) ($p = 0.047$).

Table 5: *Comparison of HIV negative and HIV positive patients with Bell's palsy (n=55)**

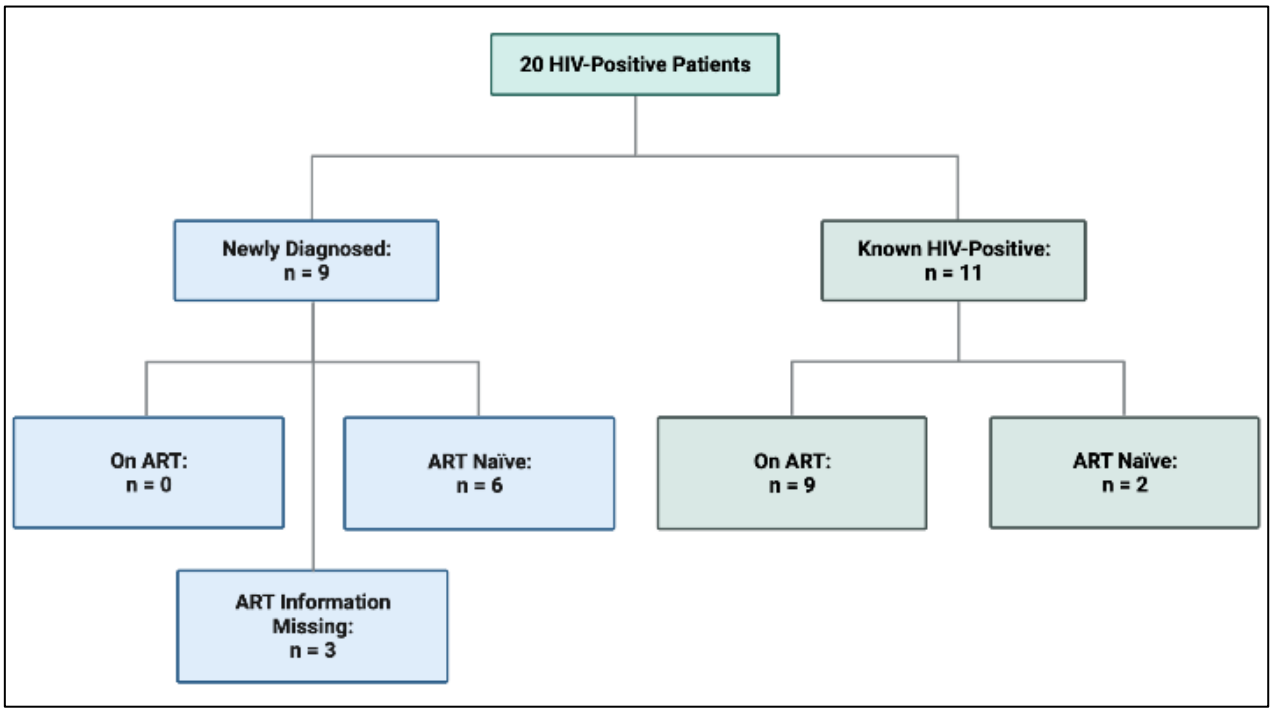
Variable	HIV negative (n=35)	HIV positive, newly diagnosed (n=9)	Known HIV positive (n=11)	p-value
Age (median, IQR)	41 (29 - 54)	40 (38 - 45)	43 (36 - 57)	0.900#
Gender				
Males	19 (54.3)	4 (44.4)	5 (45.5)	0.793α
Females	16 (45.7)	5 (55.6)	6 (54.6)	
Year of diagnosis				
2019	11 (31.4)	1 (11.1)	3 (27.3)	0.782α
2020	9 (25.7)	2 (22.2)	3 (27.3)	
2021	15 (42.9)	6 (66.7)	5 (45.5)	
Season				
Summer	12 (34.3)	0 (0.0)	2 (18.2)	0.047α
Autumn	14 (40.0)	2 (22.2)	3 (27.3)	
Winter	6 (7.1)	4 (44.4)	2 (18.2)	
Spring	3 (8.6)	3 (33.3)	4 (36.4)	
Side of face				
Left	17 (48.6)	5 (55.6)	1 (9.1)	0.025α
Right	16 (45.7)	3 (33.3)	10 (90.9)	
Bilateral	0 (0)	1 (11.1)	0.0	
Unknown	2 (5.7)	0 (0)	0 (0)	
Any co-morbidities	*11 (31.4)*	*4 (44.4)*	*0 (0.0)*	*0.031α*
Diabetes mellitus	10 (28.6)	2 (22.2)	0 (0.0)	0.112α
HbA1c	6 (5.4- 7.9)	5.5 (5.1- 6.1)	5.8 (4.8- 5.9)	0.156#

**Excludes three individuals for which HIV status is unknown; IQR = interquartile range; #K-test for equality of medians p-value, α = Fischer's exact p-value*

The clinical characteristic of the side of face involved also had a statistically significant distribution as evidenced by a p-value of 0.025, with the right side being involved in more than half of the patients. Known HIV positive patients were much more likely to present with right sided weakness (90.9%) compared to HIV negative patients who were just as likely to have left or right sided weakness and newly diagnosed HIV positive patients who

were slightly more likely to have left sided weakness. As noted, one newly diagnosed HIV positive patient had bilateral facial weakness. Individuals who were newly diagnosed HIV positive had the highest frequency of co-morbidities other than HIV compared to HIV negatives or known HIV positives. Among the HIV negatives and newly diagnosed HIV group, diabetes was the most common underlying condition.

Figure 2: *Breakdown of the HIV positive subgroup with regards to the timing of HIV diagnosis in relation to Bell's palsy diagnosis as well as ART information*



Among those who were known HIV positive and on ART at Bell's diagnosis (n=9; 81.2%), the median year of ART start was 2017 (IQR 2011 – 2019). The median duration on ART was three years (IQR 0.5 – 9.4 years). Of the nine on ART at Bell's diagnosis, 8/9 were on first line ART – Tenofovir/Lamivudine/Efavirenz (TLE, n=5) OR Tenofovir/Emtricitabine/ Efavirenz (TEE, n=2) OR Tenofovir/Lamivudine/Dolutegravir (TLD, n=1) while one was on a second line ART containing "Kaletra" ("Aluvia").

***Table 6**: Description of HIV positive patients, comparing newly diagnosed HIV positive patients to known HIV positive patients (n=20)*

Variable	HIV positive, newly diagnosed (n=9)	HIV positive, known (n=11)	p-value
CD4			
CD4 count at HIV diagnosis (mean, SD)	243 (83)	278 (148)	0.670#
CD4 count at BP diagnosis (mean, SD)	243 (83)	335 (326)	0.553#
Viral Load (VL)			
Log VL at HIV diagnosis	4.4 (3.7-5.0)	2 (0-4)	0.157α
VL at HIV diagnosis	32475 (5615-111000)	100 (1-10000)	0.157
Log VL at BP diagnosis	4.4 (3.7- 5.0)	3.1 (1.4-4.1)	0.089α
VL at BP diagnosis	32475 (5615-111000)	1447 (28-17337)	0.089
ART			
ART naïve	6 (66.7)	2 (18.2)	0.001α
On ART	0 (0.0)	9 (81.2)	
ART information missing	3 (33.3)	0 (0.0)	

IQR = interquartile range; SD = standard deviation; # = Student's t-test p-value; α = Wilcoxon rank sum test p-value

Due to lost specimens and patients that didn't follow-up, the CD4 and VL data is incomplete. In the newly diagnosed HIV positive group, four patients' CD4 & VL were unknown, while nine of the known HIV positive patients had incomplete data in this regard. Among those who had CD4 count data available, HIV positives newly diagnosed were similar to known HIV positives with respect to CD4 count at Bell's diagnosis and at HIV diagnosis.

Figure 3: *CD4 counts at diagnosis of HIV and Bell's palsy by HIV status*

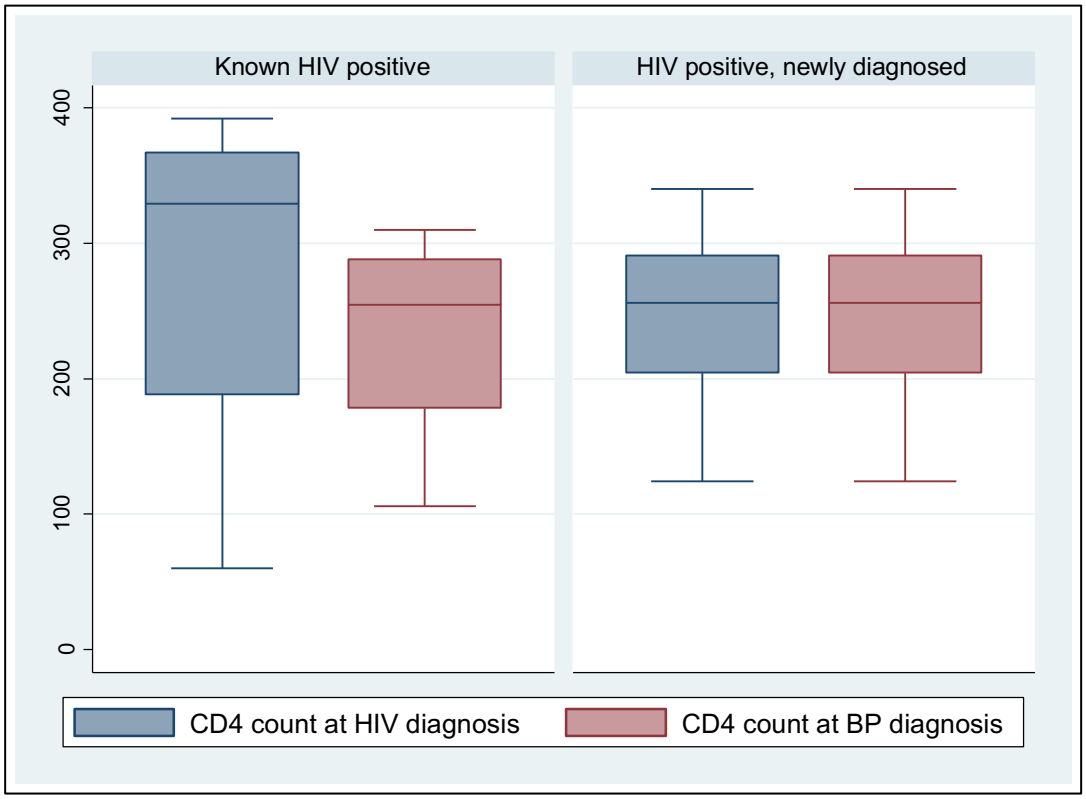
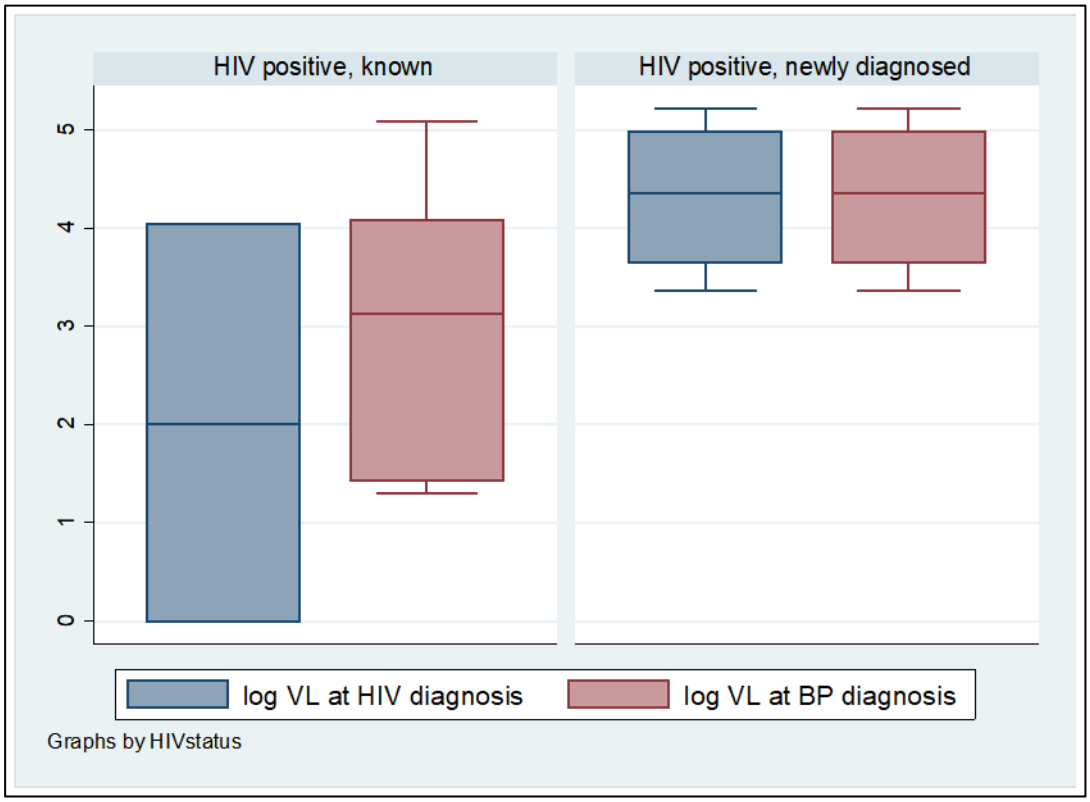


Figure 3 visually shows the spread of the CD4 values, with a median CD4 of 329 cells/μL in the known HIV group (IQR 188 – 367 cells/μL) at the time of HIV diagnosis (available for 4/11), contrasted with a median of 276 cells/μL (IQR 178 – 291 cells/μL) of the same group at time of Bell's diagnosis (available for 10/11). The newly diagnosed HIV group (with HIV being diagnosed at the time of Bell's diagnosis) had a median CD4 of 256 cells/μL (IQR 204 – 291 cells/μL) at the time of diagnosis (available for 5/9).

Figure 4: *Viral loads at diagnosis of HIV and Bell's palsy by HIV status*



Among those who had VL data available, the spread of the VL is shown in **Figure 4**. In the known HIV positive subgroup, the median VL at time of HIV diagnosis was 100 copies/mL (IQR 1 – 10000; LogVL of 2 with IQR 0 – 4) and 1447 copies/mL (IQR 28 – 17337; LogVL of 3.1 with IQR 1.4 – 4.1) at the time of Bell's diagnosis. In the newly diagnosed HIV positive group, the median VL was 32475 copies/mL (IQ 5615 – 111000; LogVL 4.4 with IQR 3.7- 5.0) at time of presentation. The differences in these values were not statistically significant.

2.6 Analysis and discussion

This present study mainly focused on the HIV frequency, but a few other characteristics and associations have also been observed and commented on below.

2.6.1 Demographics

The mean age for this cohort, 42.2 years, corresponds with international data[59,63] and did not show a significant age difference between the HIV positive and negative subgroups. This is however at variance with other studies conducted in Africa that reported a younger mean age.[51,52] Komolafe et al. found a significantly lower age in HIV positive patients (29.15 years) as compared to HIV negative patients (44.39 years).[52] In contrast to this lower age of presentation, a population-based study conducted in Asia by Kim and Park, published in 2021, found the highest incidence in patients in their sixties, ascribing it to an aging society, increased access to medical resources and lifestyle changes in their population.[72] Sathirapanya et al. studied peripheral facial weakness in HIV positive patients, and also found a higher median age.[63] According to Magazi et al. the reason for a younger age of presentation in their study has not been explained thus far, but mentioned that their population group consisted of patients coming from a poorer part of the community.[51] This latter comment, contrasted with the conclusion by Kim and Park noted above, suggests that socio-economic factors might play a role in the age of presentation of Bell's. It should also be kept in mind that South Africa has the largest concentration of HIV positive patients in the world[73] with the highest prevalence being in adults 15 – 49 years of age.[44]

There was no significant gender predilection, thereby reflecting literature, with only slightly more females than males in the HIV positive subgroup (11 vs 9), and slightly more males in the HIV negative group (19 vs 16).

2.6.2 Clinical characteristics

The only clinical characteristic evaluated was the side of the face involved. There was an interesting, yet unexplained, association between the side of the face involved and being known with HIV prior to presentation with Bell's, with 90.9% of this known HIV positive subgroup having had right sided facial weakness. In a Nigerian study it was also found that right sided weakness was more common in the HIV positive subgroup (not specified whether newly diagnosed or known HIV), with 61.5% of the HIV positive patients that had right sided weakness.[52] A Togolese study by Balogou however found left sided weakness to be more common, even in the HIV positive subgroup.[57] The reason for the predominant right sided weakness found in the known HIV positive group in this study is unknown.

The one patient that had isolated bilateral facial weakness (without other clinical, electrophysiological, serological or imaging findings suggestive of an alternative diagnosis) was newly diagnosed HIV positive at the time of presentation with facial weakness, a finding that is in accordance with literature indicating that bifacial weakness in the setting of HIV is likely to occur in the early stage of HIV [63, 69]

2.6.3 HIV and Bell's Palsy

Neurological complications in a clade C HIV population, like the population this study was conducted in, are as high as 75%,[40] with facial palsy being the most frequently encountered cranial neuropathy during any stage of HIV infection.[49] The frequency of HIV in this study is 34.5%. In the literature there is a wide range in the HIV frequency in patients with facial paralysis, ranging from 25%[70] to 89.1%[71] There also seems to be geographical variations with tropical countries showing an association between HIV and Bell's, but none from Sahel countries.[57, 64, 71] Further illustrating a geographical variation is the observation by Peitersen in a Danish study that only found four cases of AIDS out of 2570 cases of facial palsy.[54] Conversely to the frequency of HIV in Bell's as evaluated in our study, a low frequency of Bell's in HIV positive patients was found in countries where HIV is not endemic, namely 1% by Riancho et al. in Spain,[49] and 0.26% by Sathirapanya et al. in Thailand.[63]

Although data in the literature spans a long period of both pre- and post-ART era, there is no clear trend in the frequency to suggest an influence by ART, neither follow-up studies in the same populations to evaluate regional fluctuations. In another study by Magazi et al. which was conducted in a similar population, they found a significantly higher frequency of HIV (72.3%) as compared to the present study.[74] The much shorter study period in our study and the influence of the COVID-19 pandemic on the referral and access to specialist clinics might have played a role in this regard.

In this study the author found both newly diagnosed and known HIV positive patients with the latter subgroup representing just over half of all the HIV positive patients, largely

reflecting literature that indicates that HIV-associated Bell's can occur in any stage of the disease.[49,63] In the series by Sathirapanya et al. that evaluated HIV positive patients identified over a thirteen-and-a-half-year period in Thailand, they found that HIV-associated unilateral Bell's more commonly occurred long after the diagnosis of HIV and that 7/11 of their patients diagnosed with HIV prior to presentation with Bell's were on ART.[63] As alluded to, 11/20 HIV positive patients in this study were previously diagnosed with HIV (prior to presentation with facial weakness) and that 81.2% of these patients were on treatment (mostly first line), raising the possible deduction that ART does not prevent Bell's in HIV. Furthermore, literature has thus far not confirmed a beneficial effect of ART on the facial weakness.[63]

Davenport et al. reported that the outcome of Bell's was not improved by antiviral drugs in non-HIV-associated cases, despite the suspected reactivation of HSV, but that steroids were associated with improvement.[75] Considering the similarities in presentation, a suspected role of viruses and response to treatment with steroids, in both HIV-associated[49] and non-HIV-associated Bell's,[75] with a postulated immune mediated pathophysiological process in HIV-associated cases as well,[63] it seems that ART in HIV patients does not necessarily prevent nor improve facial weakness in HIV-associated Bell's palsy.

The CD4 cell count can be used as a measure of immunocompetence in HIV positive patients and tends to deplete with progression of disease.[33] The WHO classifies a CD4 count below 200 as severe immunodeficiency, whereas a CD4 200 – 349 cells/μL is said to be moderate immunodeficiency.[76] The mean CD4 cell count at the time of Bell's diagnosis in this study was more than 200 cells/μL. Furthermore, the difference in mean

CD4 count between known and newly diagnosed HIV positive patients was less than 100 cells/μL. Despite the range of CD4 counts in the setting of facial palsy found in literature, a mean CD4 of more than 200 at the time of presentation with facial weakness and HIV was a consistent finding.[49, 52, 56, 63, 64] This association is understandable if one again considers HIV-related Bell's to be, at least in part, involving an immune mediated process as alluded to in the literature review. Severe immunosuppression and an associated lower CD4 count have a more diverse aetiology and include infections, lymphoma and other tumors.[49]

2.6.4 Other co-morbidities

In the clinical analysis by Zhao et al. they presented that diabetes mellitus was the most common co-morbid condition.[50] Psillas et al. also noted a higher incidence of diabetes mellitus, hypertension and hypercholesterolaemia in patients with Bell's, with diabetes having the highest incidence.[77] This association between type 2 diabetes and Bell's has also been suggested by the data in this current study, reflected in the finding that 10 out of the 11 patients in the HIV negative group with co-morbidities had diabetes mellitus.[54] In this context it is furthermore important to note that only two of the 20 HIV positive patients, both newly diagnosed HIV positive, had diabetes mellitus as well. It can consequently not be concluded that HIV was the only associated aetiology or cause of the facial weakness in these two patients. More data is thus needed to remove the effect of diabetes in the setting of concurrent occurrence of HIV and diabetes mellitus with Bell's palsy.

2.7 Limitations

- The limited number of patients and study period that had to be extended.
- Not all the information of each patient was available, some due to lab errors and lost specimens, others due to patients that did not follow-up as requested.
- Not enough data to remove or adjust for the impact of diabetes mellitus, especially in the HIV positive subgroup with co-morbidities.

2.8 Conclusion

HIV is associated with Bell's palsy and can be the initial presenting problem in HIV infection. It can also occur in the later stages of the HIV disease course in patients on ART. The mean CD4 at the time of presentation with Bell's palsy is > 200 cells/μL, whether newly diagnosed or known with HIV prior to presentation. For unknown reasons, right sided weakness is significantly more common in patients previously diagnosed with HIV. Furthermore, diabetes mellitus is a common co-morbidity associated with Bell's in HIV negative patients.

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3 CHAPTER 3: APPENDICES

Appendix i: Data capturing sheet

DATA CAPTURING SHEET

GENDER		MALE		FEMALE
AGE				
STUDY NUMBER				
DATE OF DIAGNOSIS OF BP				
SIDE OF FACE INVOLVED		LEFT	RIGHT	BILATERAL
HIV STATUS		POSITIVE		NEGATIVE
IF HIV POSITIVE				
	DATE OF DIAGNOSIS OF HIV			
	CD4 AT DIAGNOSIS OF HIV			
	VL AT DIAGNOSIS OF HIV			
	CD4 AT DIAGNOSIS OF BP			
	VL AT DIAGNOSIS OF BP			
	IF ON TREATMENT: 1. REGIMEN			
	2. DATE COMMENCED			
HbA1c (%)				
TPHA		POSITIVE		NEGATIVE
RPR		POSITIVE		NEGATIVE
ANA		POSITIVE		NEGATIVE

Explanation of abbreviations and diseases tested for with investigations above:
***BP**: Bell's Palsy*
***HIV**: Human Immunodeficiency Virus*
***VL**: Viral Load*
***HbA1c**: Haemoglobin A1c: Indication of average serum glucose of past three months (Diabetes Mellitus)*
***TPHA**: Treponema Pallidum Haemagglutination Assay (Syphilis)*
***RPR**: Rapid Plasma Reagin (Syphilis)*
***ANA**: Antinuclear Antibodies (Auto-immune diseases)*

FACULTY OF HEALTH SCIENCES

Dr. J.C. Visagie: University of Witwatersrand; Department of Neurology; CMJAH

Appendix ii: Informed consent forms

INFORMED CONSENT:
PARTICIPATION IN STUDY

THE FREQUENCY OF HIV IN PATIENTS WITH NEWLY DIAGNOSED BELL'S PALSY AT A TERTIARY CENTRE

I confirm that I have been informed by dr. Jan Christoffel Visagie/other doctor about the nature of the study. The information sheet was read to me. I understand the information and had the opportunity to ask questions.

I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. I understand that if I choose not to give consent, this will not affect my treatment in any way.

I understand that dr. Jan Christoffel Visagie/other doctor will ask me questions about my facial weakness and other relevant systemic enquiry, as well as my past medical history. I am aware that he/she will do a full neurological examination on me. Furthermore, I am aware that a blood sample might be taken (see "Information sheet").

I agree to take part in above mentioned study and I hereby give consent to an interview and neurological examination.
I also consent for blood to be taken and the use of the results and information for research purposes.

Full name, surname of patient	Signature/Thumb print	Date
Name of translator or other person explaining informed consent (designation)	Signature	Date
Witness 1	Signature	Date
Witness 2	Signature	Date

Dr. J.C. Visagie: University of Witwatersrand; Department of Neurology; CMJAH

INFORMED CONSENT:
HIV TEST

THE FREQUENCY OF HIV IN PATIENTS WITH NEWLY DIAGNOSED BELL'S PALSY AT A TERTIARY CENTRE

I,_____ (full name), an adult male/female from _____ (address) hereby confirm that I have been informed by dr. _____ about the reasons, nature, conduct, benefits, risks and implications of this HIV test. I have received and understood all the relevant information concerning the proposed test. I have also had sufficient opportunity to consider the options in light of the information provided and to ask questions before proceeding with the test. I therefore freely and voluntarily agree to the HIV test being performed, which includes the drawing of a blood sample and a test being performed on that sample. I agree that dr. _____ will inform me of the results of the test in person. I hereby agree that the results of the test may be anonymously used for purposes of research and/or data collection purposes, provided that such information is de-identified with sufficient safeguards. I know that I am, at any stage, free to withdraw my consent to undergo this test.

Full name, surname of patient	Signature/Thumb print	Date
Full name, surname of doctor	Signature	Date
Witness 1	Signature	Date
Witness 2	Signature	Date

Dr. J.C. Visagie: University of Witwatersrand; Department of Neurology; CMJAH

Appendix iii: Ethics Clearance Certificates (for the study and telephonic consent)

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr JC Visagie
School of Clinical Medicine
Department of Neurosciences
Division of Neurology
Charlotte Maxeke Johannesburg Academic Hospital

E-mail: visagie.christoff@gmail.com

CC: Supervisor: Professor G Modi <Girish.Modi@wits.ac.za>
and <HREC-Medical ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/03/23

REF: *R14/49*

PROTOCOL NO: **M191137** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *The frequency of Human Immunodeficiency Virus (HIV) in patients with newly diagnosed Bell's Palsy at a tertiary centre*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2020/06/29

Dr JC Visagie
School of Clinical Medicine
Department of Neurosciences
Division of Neurology
Charlotte Maxeke Johannesburg Academic Hospital

Sent by e-mail to: visagie.christoff@gmail.com

Dear Dr Visagie

Re: **Protocol Ref No: M191137**
Protocol Title: *The frequency of Human Immunodeficiency Virus (HIV) in patients with newly diagnosed Bell's Palsy at a tertiary centre*
Principal Investigator: Dr JC Visagie

Thank you for your e-mail of 2020/06/17.

I confirm that your proposal to get patient consent telephonically, rather than in person, to access their hospital records has been noted and approved.

Thank you for keeping us informed.

Yours Sincerely

J. Burns

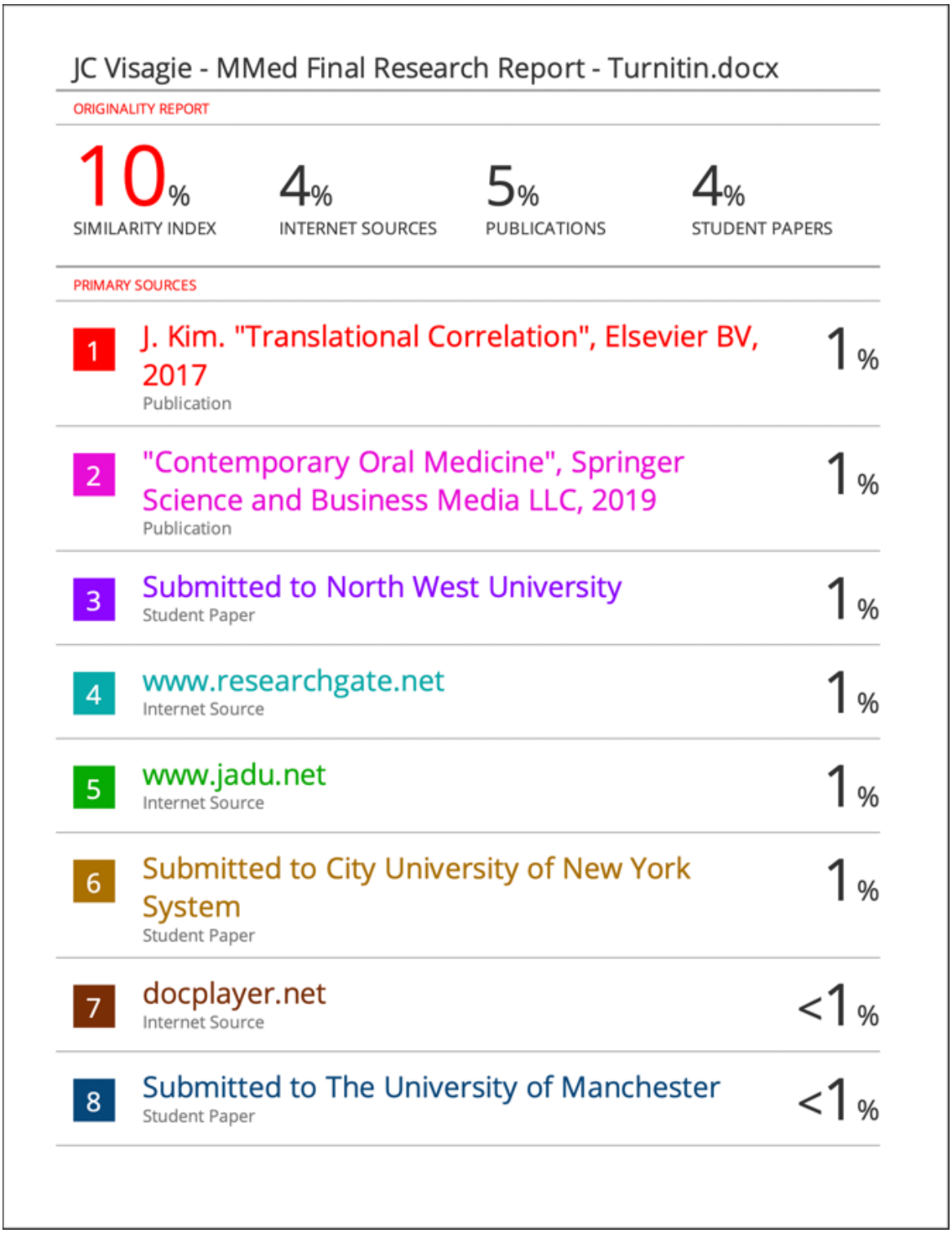
Mr I Burns
For the Human Research Ethics Committee (Medical)

CB Penny

Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

Appendix iv: Plagiarism Report

The plagiarism software “Turnitin” was used to determine the similarity index of this research report, which was 10%. This relates to the use of standardized terms and definitions. All other information has been appropriately referenced.



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