HIV-Polymyositis progressing to inclusion body myositis: clues to earlier diagnosis

by

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List of abbreviations

HIV	Human Immunodeficiency Virus
ART	Anti-retroviral therapy
PM	Polymyositis
IBM	Inclusion Body Myositis
CK	Creatine Kinase
MRC	Medical Research Council
IMNM	Immune mediated necrotizing myopathy
LDH	Lactate Dehydrogenase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
EMG	Electromyography
SD	Standard Deviation
COX	Cytochrome c oxidase
SDH	Succinate Dehydrogenase
ENMC	European Neuromuscular Centre
MHC	Major histocompatibility complex
NSM	Non-specific myositis
GSH	Groote Schuur Hospital
HREC	Human Research Ethical Committee
TUG	Timed Up and Go
FRC	Functional rating scale
No.	Number
IQR	Interquartile Range
TLD	Tenofovir, lamivudine and dolutegravir
FMB	First muscle biopsy
SMB	Second muscle biopsy
CT	Connective tissue
RRF	Red ragged fibre
MYO	ATPase Myosin ATPase
PAS	Periodic acid Schiff
FRC	Functional Rating Scale
JH	Jeannine Heckmann
BBR	Bhuvaneshlal Basant Rai
GSH	Groote Schuur Hospital
HGD	Hand grip dynamometer

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Abstract

Background

Inflammatory myopathies in Human Immunodeficiency Virus (HIV)-positive patients may include polymyositis (PM), dermatomyositis and inclusion body myositis (IBM). Although PM is still mentioned, it is thought to be rare since the discovery of myositis autoantibodies. In the last few years it has been reported that several cases who were initially diagnosed as HIV-associated PM (HIV-PM) clinically and on muscle biopsy, change into a treatment-resistant HIV-IBM clinical phenotype. These cases are referred to as HIV-PM/IBM overlap syndrome. In recent years at Groote Schuur Hospital (GSH), we have also encountered patients with HIV-PM/IBM.

Aims

The aims of our study were: (1) to describe the demographic, clinical and laboratory findings in patients that were being treated for refractory “PM” and in whom the clinical diagnosis was changed from HIV-PM to HIV-IBM at the neurology unit, Groote Schuur Hospital (GSH) (2) to identify the earliest clues for this progression from HIV-PM to HIV-IBM.

Methods

A retrospective folder review was conducted for nine patients with HIV-IBM who interacted with the neurology service at GSH from 1 January 2000 to 30 November 2023. The duration between the diagnosis of PM and when they first satisfied the diagnostic criteria of IBM by their case notes were recorded.

Results

All the patients were female with a median age of 50 years at IBM diagnosis. Proximal lower limb weakness was the initial complaint of all of our patients with median age of 36 years. The median maximum CK recorded was 2500 IU/L. None of the patients had a recorded CK of more than 15 times the upper limit of normal. The median interval between symptom onset to IBM diagnosis was 11 years (range: 6-15) and the median interval between PM diagnosis and IBM diagnosis was 9 years (range: 3-14). Patients were examined after a median symptom duration of 12 years. After approximately 1.5 years of follow up, two of six patients already satisfied the ENMC 2011 clinical criteria for IBM. Of the most severely affected muscles in the lower limbs with Medical

Research Council (MRC) muscle power grades of 0-2 (out of 5), the knee extensors were most frequent (≥ 90% of cases). In the upper limbs, the finger flexors were the most involved with moderately weak muscles in 50% of cases. Four (44.4 %) patients reported mild dysphagia at IBM diagnosis visit. Seven of nine patients received immunotherapy. All patients who received any form of immunosuppressive therapy received prednisone (median duration: 137 months [(range: 24-180)]). The median number of immunosuppressants used by patients who received any form of immunotherapy (n=7) was four. All nine patients had muscle biopsies between 12 and 35 months after onset of symptoms. The most important findings were that all patients had evidence of inflammatory infiltrates. An increase in MHC 1 expression and mitochondrial abnormalities (i.e COX – /SDH + fibres) were noted in all four patients in whom immunohistochemical staining and combined SDH and COX staining were performed. At the visit to neurology, five patients could be categorized as clinically defined IBM and four were defined as clinically probable IBM.

Conclusions

Earlier recognition of this progression from HIV-PM to HIV-IBM was not possible due to poor awareness of this entity. Three of our HIV-IBM patients were younger than the age criteria for non-HIV sporadic IBM at the IBM visit. As all these patients had otherwise typical IBM features but were younger, the age criteria of ENMC 2011 may not be applicable to HIV-IBM patients. Only four patients subjectively and objectively responded to immunosuppressive treatment for a short median period of 22 months (range: 8-53). Drug refractoriness should alert the clinicians of this clinical progression from HIV-PM to HIV-IBM. A relatively high CK but less than 15 times the upper limit of normal is another clue for this clinical entity. In this study all the patients who had COX/SDH staining showed marked COX negative and SDH positive fibres and hence this test should be performed in all inflammatory myopathy muscle biopsy samples for earlier recognition of HIV-IBM.

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BACKGROUND AND LITERATURE REVIEW

Introduction

Human Immunodeficiency Virus (HIV) not only affects the immune system, but also gains access to the host's nervous system soon after infection. Neurological involvement related to HIV can occur throughout the course of infection [1, 2] and includes opportunistic infections, stroke, dementia, myelopathy, peripheral neuropathies, antiretroviral therapy (ART) related complications and myopathies. [3] HIV-associated myopathy may occur from several causes, including zidovudine therapy (toxic myopathy), inflammatory myopathy (HIV-myositis) and rarely opportunistic infection (pyomyositis). [4]

Inflammatory Myopathies

Inflammatory myopathies are a group of diseases in which inflammation occurs in muscles. They are characterized by muscle weakness, elevated muscle enzymes, and findings of immune dysfunction on muscle biopsies. The old classification of inflammatory myopathies focused on polymyositis (PM) [5-8], dermatomyositis [9] and inclusion body myositis (IBM). Although PM is still mentioned, it is thought to be rare. In the last 15 years with the discovery of muscle specific autoantibodies and distinct histopathologic subgroups, a new classification criteria for inflammatory myopathies developed. It included dermatomyositis, immune-mediated necrotizing myopathy, IBM, anti-synthetase syndrome, and overlap myositis. [10-12]

Table 1 shows old and new classification of inflammatory myopathies [13]

Old Nomenclature	**Polymyositis**			**Dermatomyositis**	**IBM**
New Nomenclature	Anti-synthetase syndrome*	Immune Mediated Necrotising Myopathy*	Overlap Myositis*	Dermatomyositis	IBM

*** based on myositis specific antibodies and muscle biopsy findings**

Polymyositis

Polymyositis (PM) is much less common than originally thought because a large proportion of patients who were initially diagnosed with PM have subsequently been diagnosed with anti-synthetase syndrome without a rash, an immune mediated necrotizing myopathy (IMNM) and overlap myositis based on clinical features, autoantibodies, and histopathology results. Although PM is increasingly controversial as a distinct entity, we shall refer to PM when referring to non-necrotizing myositis (i.e anti-synthetase syndrome and overlap myositis).

The old diagnostic criteria for PM from 1975 by Bohan and Peter [14] includes a combination of several findings. Clinically the patient may have had a subacute onset of progressive, symmetrical weakness of the limb-girdle muscles. Muscle biopsy showed endomysial inflammatory infiltrate with CD8+ T cell predominance. Laboratory tests showed elevation of creatine kinase (CK), lactate dehydrogenase (LDH), aldolase and transaminases (i.e. alanine transaminase (ALT) and aspartate transaminase (AST)). Electromyography of the weak muscles showed features of an irritable myopathy i.e. short duration, low amplitude polyphasic motor unit action potentials, fibrillation potentials and complex repetitive discharges.

Some authors have recognised the prominent mitochondrial pathology in a subset of idiopathic inflammatory myopathy patients. [15] Although those patients had no rimmed vacuoles on muscle biopsy and responded transiently to immunosuppressive therapy, up to half of the patients who were initially diagnosed as treatment-responsive non-specific myositis with mitochondrial abnormalities, later progressed to treatment-refractory IBM. The study concluded that non-specific myositis with mitochondrial pathology may be considered as a possible early form of IBM.

Further discussion regarding the more recent subcategories of myositis previously referred to as PM will now follow.

a) Anti-Synthetase Syndrome

Anti-synthetase syndrome is a rare multisystematic autoimmune disease characterized by interstitial lung disease, myositis, arthritis and is associated with eight serum autoantibodies to the aminoacyl transfer RNA synthetases (anti-PL-7, anti-PL-12, anti-Jo-1, anti-EJ, anti-OJ, anti-KS, anti-Zo, and anti-Ha).

b) Overlap Myositis

Overlap myositis is defined as the combination of myositis and another rheumatic diseases such as systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis or Sjogren syndrome. The common overlap myositis associated antibodies are anti-Ro52 antibodies, Anti-PM-Scl antibodies, Anti-ku and Anti-U1 RNP antibodies. Arm abductors are typically weaker than hip flexors in cases of overlap myositis with anti–PM-Scl antibodies. [16]

Dermatomyositis

Dermatomyositis is characterised by subacute onset of symmetric, proximal muscle weakness and a group of characteristic skin manifestations such as heliotrope rash, Gottron's sign (erythematous macules and patches over the back of the fingers, elbows or knees), shawl sign, mechanic hands, poikiloderma and calcinosis cutis. [9] Aside from the skin involvement, systems other than skeletal muscle like gastrointestinal, pulmonary, cardiac and joint systems could be involved. In some cases, it is even associated with malignancy. There are five known dermatomyositis-specific autoantibodies. They are anti-MI-2 (associated with a good prognosis and low malignancy risk), antinuclear matrix protein/ anti-NXP-2 (associated with subcutaneous calcification and increased risk of malignancy in adults), anti transcription intermediary factor 1-γ /anti-TIF1γ (associated with malignancy and severe skin lesions), antimelanoma differentiation-association protein/anti-MDA-5 (minimal muscle involvement but rapidly progressive interstitial lung disease and associated with a poor prognosis), and anti-small ubiquitin-like modifier activating enzyme/anti-SAE (usually minimal muscle involvement).

Immune Mediated Necrotising Myopathies (IMNM)

IMNM are clinically characterized by severe proximal muscle weakness with rare extra-muscular manifestations and markedly elevated CK levels. Onset may be abrupt. Muscle biopsy typically shows predominantly muscle fiber necrosis with the absence of clear inflammation. [17] The main antibodies associated with IMNM are the anti-HMG-CoA reductase/anti-HMGCR (associated with history of statin exposure) and anti-signal recognition particle SRP/anti-SRP antibodies (more severe myopathy).

Inclusion Body Myositis

IBM is an often-misdiagnosed myopathy subtype. Since IBM often affects older adults, the symptoms of insidious and progressive weakness may be attributed to aging, resulting in under recognition. [14] IBM can be distinguished from other inflammatory myopathies by the asymmetric and distal muscle involvement with predilection for wrist or finger flexors in the upper limb and knee or foot extensors in the lower limb and by its insidious onset and wasting of finger flexors, quadriceps and wrist flexors. The common early complaints of IBM patients are difficulty to stand up from a sitting/lying position or sometimes requiring push up from the arm rest, struggling to climb stairs, recurrent falls due to knee giving way (quadriceps weakness) or frequent tripping (ankle dorsiflexion weakness). Hand grip weakness will impact manual dexterity (difficulty in opening bottle caps, tying shoelaces, buttoning and writing). Dysphagia is common in IBM. [18]

The clinical signs that one should look for in the early detection of IBM are asymmetric atrophy of the quadriceps and medial forearm flexors muscles and finger flexor weakness which is disproportionately greater than that of the hip flexors and shoulder abductors, respectively. In most IBM cases the flexor digitorum profundus muscle is the first muscle to be involved and is disproportionately weaker than other hand muscles. This important sign can be picked up by testing the flexion at the distal interphalangeal joints of finger flexors. Sparing of the hypothenar and thenar muscles helps distinguish IBM from the split hand asymmetrical weakness of amyotrophic lateral sclerosis.

The key muscle biopsy histopathological findings in IBM patients are endomysial inflammatory infiltrates with partial invasion, rimmed vacuoles, tubulofilaments on electron microscopy, sarcolemmal upregulation of MHC 1 expression, protein aggregates and mitochondrial abnormalities (COX negative/ SDH positive fibres). [19]

Although the term IBM was first used in 1971 [14], the first formal diagnostic criteria for IBM were proposed in 1990s and subsequently the ‘Griggs’ criteria became the established benchmark in 1995. [14, 20] However, the ‘Griggs’ criteria lacked sensitivity as the diagnosis of definite IBM can only be made if all three of the following pathological features are present, independent of the clinical features, i.e. inflammatory infiltrate with partial invasion of muscle fibre, rimmed vacuoles and either

amyloid deposits or 15 to18 nm tubulofilaments. Since the 'Griggs' criteria were established in 1995, there have been several proposals for revised diagnostic criteria such as is outlined in Table 2.

Table 2: International diagnostic criteria for IBM- European Neuromuscular Centre (ENMC) Workshop 2011. [21]

Mandatory Criteria:
1. Age of symptom onset ≥ 45 years
2. Duration of symptoms ≥12 months
3. Serum creatine kinase level ≤15x upper limit of normal
Clinical Criteria:
1. Quadriceps weakness > hip flexors weakness.
2. Finger flexors weakness > shoulder abductors weakness.
Pathological Criteria:
1. Endomysial inflammatory infiltrate
2. Rimmed vacuoles
3. Protein accumulation or 15-18nm filaments
4. Upregulation of MHC class I
Classification categories:
1. **Clinicopathologically defined IBM:** Mandatory criteria + ≥ 1 clinical criteria + pathological criteria 1,2 and 3
2. **Clinically defined IBM:** Mandatory criteria + all clinical criteria + ≥ 1 pathological criteria
3. **Probable IBM:** Mandatory criteria + 1 clinical criteria + ≥ 1 pathological criteria

The pathogenesis of IBM is unknown, but probably consists of an interplay between degenerative and inflammatory pathways. [22] Compared to the other inflammatory myopathies, there is no proven therapy to stop or even slow progression of IBM. [23] The recent identification of anti-cytosolic 5'-nucleotidase 1A antibody biomarker [24] and the ability of muscle imaging like magnetic resonance imaging [25] to detect patterns of preferential muscle involvement which may not be evident on clinical

evaluation in IBM patients without HIV-infection, has allowed for earlier diagnosis of the disease than what was previously possible.

Muscle Biopsy findings of Inflammatory Myopathy

A muscle biopsy is not only important to confirm the diagnosis of inflammatory myopathy but also to classify it into different subtypes and distinguish it from other noninflammatory myopathies. The common histological finding to all subtypes except IMNM is the presence of inflammatory infiltrate in the muscle tissue.

There are some key distinct features for each subtype. Perifascicular muscle fibre atrophy, perifascicular MHC 1 positive fibre and perifascicular reduced cytochrome c oxidase (COX) stain fibre with predominant perimysial/perivascular CD4+ T-cells favour a diagnosis of dermatomyositis. IMNM show minimal or no inflammation, marked muscle fibre necrosis with regenerating fibres and minimal MHC1 expression on non-necrotic fibres. The distinctive histological features of all inflammatory myopathies are shown in table 3.

Muscle biopsies from patients with mitochondrial myopathies often show a scattered picture of COX-deficient and normal reacting, COX-normal fibres. The prominent blue fibres seen on a combined COX/SDH (succinate dehydrogenase) histochemical stain strongly indicate the presence of a genetic defect involving the mitochondrial genome and is common in IBM patients. [26]

Table 3: The muscle biopsy features of inflammatory myopathies [17, 27]

Findings	Overlap myositis	Antisynthethase syndrome	Dermatomyositis	IBM	Immune-mediated necrotising
Inflammatory infiltrates	Endomysial/ perivascular/ perimysial	Endomysial	Perivascular /interfascicular	Endomysial	Minimal or absent
Inflammatory T cells subtypes	CD8+	CD8+	CD4+	CD8+	Absent
Partial invasion of non-necrotic muscle fibres	Present	Present	Absent	Present	Absent
Fragmentation of perimysium and perifascicular muscle fibers	Absent	Present	Absent	Absent	Absent
Necrotic fibres	Minimal and scattered	Minimal and scattered	Minimal and scattered	Minimal and scattered	Extensive
Intranuclear actin like filaments	Absent	Present	Absent	Absent	Absent
Tubulofilaments	Absent	Absent	Absent	Present	Absent
Perifascicular atrophy	Absent	Absent	Present	Absent	Absent
MHC-1 expression	++	++	++	+++	+/-
Rimmed vacuole	Absent	Absent	Absent	Present	Absent
Increased perimysial and/or endomysial connective tissue	Minimal	Minimal	Minimal	Marked	Marked
Mitochondrial abnormalities (COX-/SDH+ myofibers)	Less common	Less common	Common	Common	Less common
Protein aggregates and Amyloid	Absent	Absent	Absent	Present	Absent

Legend: MHC, major histocompatibility complex; COX, cytochrome c oxidase negative; SDH+, succinate dehydrogenase–positive

Treatment of Inflammatory myopathies [28]

There are no standardized consensus guidelines for treatment of inflammatory myopathies due to its variable course, phenotypic differences and hence, only few randomized controlled treatment trials have been performed. The first line treatment for all inflammatory myopathies is corticosteroids except for IBM which is refractory to treatment. [20] Corticosteroids can be given either orally (prednisone 1 mg/kg/day) or intravenously (methylprednisolone 500 mg/d to 1000 mg/d for 3 to 5 days) in case of severe weakness and if a rapid induction of effect is desired. High doses of prednisone should be continued for at least 4 to 6 weeks or until clinical improvement has plateaued followed by a slow taper of 5-10 mg every 2 to 3 months. Steroid-sparing agents like azathioprine, methotrexate, mycophenolate mofetil can be added as a second line treatment to avoid the side effects associated with corticosteroids. For more refractory cases, IV immunoglobulin, rituximab, cyclophosphamide and calcineurin inhibitors such as cyclosporine and tacrolimus can be used. IMNM require aggressive treatment, stoppage of statin medications and earlier use of more than one agent. Rituximab has shown excellent results in IMNM, antisynthetase syndrome and dermatomyositis. [29]

HIV and Inclusion Body Myositis

There have been six reports of 22 HIV positive patients who developed IBM between 1980 and 2016 in the English and French literature. [22] Since then, a further 21 similar cases were reported more recently suggesting an increased recognition in just a few years. All the above studies were carried out in Brazil, United States of America and England. Table 5 shows findings of eleven cases who initially presented with what would be characterised as a HIV-PM/IBM overlap syndrome that later progressed into an overt HIV-IBM phenotype. [30]

Table 4: HIV-IBM cases reported from 1996 to 2016 (adapted from Couture et al.) [22]

Reference	Age at onset of symptoms (years)	Sex Males/ Females	Years between HIV infection diagnosis and IBM	CK (IU/L) at IBM diagnosis
Hiniker 2016 [31]	34-67	12/1	unknown	500-6000
Freitas 2008 [32]	49	1/0	unknown	2600
Lacomis 2008 [33]	55	1/0	25	2082
Dalakas 2007 [34]	36-49	4/0	1-10	465-2000
Loutfy 2003 [35]	41	1/0	10	960
Cupler 1996 [36]	30-34	2/0	1-5	612-10270

Table 4 summarizes the demographics of 22 HIV-IBM cases reported from 1996 to 2016. The median age for IBM diagnosis was 47 years, but some patients were younger than expected for IBM without HIV infection. Most of the patients (95%) were male, although in the Global North HIV-infection is more prevalent amongst men. [44] The median duration from HIV diagnosis to IBM diagnosis was 6 years. The median CK level was 1322 IU/L which is higher than blood levels reported in patients suffering from non-HIV sporadic IBM (173-717 IU/L). [37] The muscle biopsies of all 22 patients performed during their follow up satisfied the histopathological diagnostic criteria of IBM although two had initial biopsies suggestive of polymyositis. Almost half (10/22) did not satisfy the ENMC 2011 diagnostic criteria of IBM [21] at the initial presentation but satisfied the old bohan and peter criteria. [14] This suggests that HIV myositis may

be an overlapping disease that can initially present like PM and then progress to a medically refractory IBM phenotype.

Table 5: Follow up findings of 11 cases who initially presented with HIV-PM/IBM overlap syndrome and then progressed to HIV-IBM reported by Lloyd et al, 2017 (30)

Sex, male	9 (82%)
Mean age at weakness onset, years	41 (SD 9)
Average time of HIV diagnosis until noticing weakness, years	9 (SD 10)
Mean time from onset of weakness to diagnosis of "myositis", years	3.6 (SD 3.2)
Mean duration from diagnosis of HIV-myositis to IBM, years	4
Mean of the highest blood CK level for each patient, IU/L	2,796 (SD 1,592)

Abbreviation: SD, Standard Deviation

Table 5 refers to 11 patients with HIV myositis seen at the Johns Hopkins Myositis centre from 2003 to 2013. None fulfilled Bohan and Peter criteria for definite PM [14], due to the presence of distal asymmetric weakness. Furthermore, the ENMC 2011 diagnostic criteria for definite or probable IBM [21] were also not satisfied for numerous reasons, including age at onset <45, lack of amyloid deposits or CK levels greater than 15 times the upper limit of normal.

In three of the 11 patients, the weakness preceded and led to the diagnosis of HIV infection. HIV-IBM patients were mostly male. Table 5 also indicates a younger mean age at weakness onset of 41 years compared to sporadic IBM with a mean age of disease onset of 58 years. [38] The mean of the highest CK level was 2796 IU/L indicating, similarly to findings by Couture et al [22], that the blood CK level in HIV-IBM patients are higher compared to non-HIV sporadic IBM patients. On muscle biopsy,

90% had endomysial inflammation, 70% had rimmed vacuoles and 64% showed positivity for 5 nucleotidase 1A antibodies. All the patients eventually developed weakness most consistent with IBM i.e. weakness primarily affecting long finger flexors, knee extensors or ankle dorsiflexors. All the patients in this study had overlapping features of PM (proximal limb weakness, raised CK and endomysial inflammation on muscle biopsy) and IBM (distal asymmetric weakness) at initial presentation, but later progressed to an IBM phenotype which was resistant to medical treatment.

Another large biopsy study of HIV-associated myopathy patients reported that 50% of patients who were initially diagnosed with PM eventually developed IBM after a median duration of six years of follow up (Table 6). [39]

Table 6: The largest series reporting biopsy proven HIV- associated myopathy adapted from Landon Cardinal et al [39]

	Polymyositis	Inclusion Body Myositis (IBM)	Non-specific myositis	Isolated Mitochondial Abnormality	Immune-mediated Necrotising Myopathy
Total n= 50	n=18	n=3	n=12	n=12	n=1
Transformation to IBM at last follow up	50% (n=7/14)	100%* (n=3/3)	0% (0/17)	0% (n=0/12)	0% (n=0/1)

* Those 3 patients were diagnosed with IBM from the start

Table 6 refers to the muscle biopsy findings of 50 HIV-positive patients with HIV myositis performed at the Pitie-Salpetriere University hospital between 2001 and 2012. [39] Medical records were retrospectively reviewed to assess muscle disease features. The median CK level of those patients was 728 IU/L. Based on their muscle biopsy

result, the patients were classified histologically as: PM (36% of cases), IBM (7% of cases), non-specific myositis (NSM, 26% of cases), isolated mitochondrial abnormality (26% of cases) and IMNM (2% of cases). They did not describe how they differentiated these muscle biopsy features. Clinical follow-up was available for 58% of NSM and 78% of PM patients. Two NSM patients and six PM patients also had repeat muscle biopsies performed at median of 2.3 (2.1–5.9) years after first biopsy. Fifty percent of PM patients (n=7/14) progressed to IBM after six years of follow-up based on immunosuppressant resistance (n=5/7), clinical findings like finger flexors and/or quadriceps weakness (n=4/7) and histology (n=3/7) as per ENMC 2011 criteria. [21] None of the patients with NSM developed IBM.

In summary, based on the reports to date HIV-positive patients who develop myositis and have been labelled as PM, are at substantial risk to progress to a treatment refractory IBM phenotype. Compared to HIV-negative IBM cases they are often younger and have higher CK levels. In recent years at Groote Schuur Hospital (GSH), we have also encountered patients with HIV-PM/IBM and were only diagnosed after years of immune treatment. The early identification of these cases should be prioritized to prevent the use of unnecessary immune therapies.

CHAPTER 2: STUDY AIMS AND OBJECTIVES

The aims of our study were:

1. To describe the demographic, clinical and laboratory findings in patients that were being treated for refractory “PM” and in whom the clinical diagnosis was changed from HIV-PM to HIV-IBM at the neurology unit, GSH from 1st January 2000 to 30 November 2023.
2. To identify the earliest clues for this progression from HIV-PM to HIV-IBM.

Objectives included:

1. To analyse the weakness scores in different muscle groups over time to identify when the diagnostic criteria of IBM were first satisfied.
2. To describe the demographic and laboratory features in this cohort.
3. To identify the duration between the diagnosis of PM and when they first satisfied the diagnostic criteria of IBM.
4. To peruse muscle pathology results in order to revisit the histopathological indicators which would be more suggestive of IBM compared to PM.

CHAPTER 3: METHODS

3.1 Design Setting and study population

A retrospective folder review was conducted for nine patients with HIV-IBM who interacted with the neurology service at GSH from 1 January 2000 to 30 November 2023. The duration between the diagnosis of PM and when they first satisfied the diagnostic criteria of IBM by their case notes were recorded.

3.2 Inclusion and Exclusion Criteria

Inclusion criteria were: 1) fulfilment of the ENMC IBM Research Diagnostic Criteria 2011 [21] (with the exception of the age criterion), 2) History of a previous diagnosis of PM, and 3) known HIV-positive status. Exclusion criteria were: 1) high probability of another muscle disease being the cause for the presentation and 2) insufficient clinical and muscle biopsy information. Patients were identified by consultant (JH) who has special interest in neuromuscular cases.

3.3 Measures

A review of the literature on HIV-IBM was performed and a list was developed of data that needed to be captured from folder reviews. The following patient information was entered onto an anonymized coded electronic (Excel) datasheet: Age, hand dominance, history of opportunistic infection like tuberculosis, clinical features with date and age of onset of symptoms, dates of initiation of ART and regimen used, time lapse between HIV diagnosis and neuromuscular symptom onset, time lapse between HIV diagnosis and ART initiation, time lapse between symptom onset and first muscle biopsy and immunotherapy. In addition, we captured the time lapse between symptom onset and IBM diagnosis, the time lapse between PM diagnosis and IBM diagnosis, and the type, dose and duration of immunotherapy received prior to IBM diagnosis. We also noted if and when swallowing difficulty occurred. We captured manual muscle testing findings in different muscle groups over time to identify when the diagnostic criteria of IBM were first met (i.e., finger flexors weaker than shoulder abduction, knee extensors weaker than hip flexors). Results of blood investigations (such as CK, nadir CD4 count, HIV viral load, thyroid function, autoimmune screen), and muscle biopsy results were also recorded.

Hand grip dynamometer findings (to measure the maximum isometric strength of the hand and forearm muscles), timed Up and Go (TUG) assessment test (a test to assess functional mobility over time), IBM functional rating scale (FRS) to assess disease severity [40] and vital capacity were recorded at IBM diagnosis visit.

Hand grip dynamometer (HGD) testing was performed by JH and BBR as follows:- With the shoulder in an adducted position, the elbow bent at 90-degree angle, not supported by examiner's hand, the dynamometer is presented vertically. The hand dynamometer is then squeezed as hard as possible in a smooth motion without jerking. The hand grip power is repeated twice more for a total of three times and an average of the three readings is noted. The median normal values [41] for men above 35 years are 46.4 to 23.7 kg (right hand); 42.2 to 23.5 kg (left hand) and for women 29.0 to 16.4 kg (right hand); 27.3 to 15.2 kg (left hand).

The maximum score of the IBM FRS is 40, and the higher the score the better the functional status of the patient. The IBM FRS is available as Appendix 1.

Steps for TUG testing is available as Appendix 2.

3.4 Data Analysis

Statistical analysis was performed using excel. Descriptive statistics such as percentages, medians and interquartile ranges or means and standard deviations, were used to summarize the results.

CHAPTER 4: ETHICS

The names and folder numbers of all our patients were recorded with a unique study number allocated to each patient in a hardcopy folder. This folder was stored separately from any clinical and laboratory data collected in an access-controlled room in E8 (Division of Neurology). Only the study number was linked to any clinical and laboratory data collected on paper-based and electronic data capture sheets. The anonymized paper-based data capture sheets were stored in a locked cupboard in an access-controlled room in the Division of Neurology and the anonymized electronic data capture sheets were stored on a password protected computer/laptop with a secure backup system.

The study was approved by the Human Research Ethical Committee (HREC) of the University of Cape Town (HREC REF 397/2023, Appendix 3). Following HREC approval, permission to conduct the study was also obtained from the Western Cape Department of Health.

CHAPTER 5: RESULTS

Our study comprised of nine HIV myositis patients who were initially diagnosed as HIV-PM, probably based on Bohan and Peter criteria, and which later changed to HIV-IBM.

Table 7: The demographics and follow up findings of our HIV-IBM patients.

PATIENT CHARACTERISTICS	All Patients (n=9)		
	Median (IQR) or No. (%)[a]		No. with Data Available
Demographics and follow up findings			
Current age, years	50	(44-55)	9
Female Sex	9	(100)	9
Weight, kg	80	(65-84)	7
Height, meters	1.6	(1.5-1.7)	7
Previous Pulmonary TB	6	(67)	9
Age at symptom onset, years	36	(31-40)	9
HIV diagnosis to symptom onset, months	18	(3-49)	9
HIV diagnosis to ART initiation, months	1.5	(0-62)	8
Symptom onset to first muscle biopsy, months	18	(12-35)	9
Symptom onset to immunotherapy initiation, months	11	(5-12)	7
Symptom onset to IBM diagnosis, years	11	(6-15)	9
PM diagnosis to IBM diagnosis, years	9	(3-14)	9
Duration of symptoms, years	12	(9-16)	9
Dysphagia at IBM diagnosis visit, n	4	(44)	9
IBM FRS at IBM diagnosis visit, n	22	(9-24)	6
Investigations			
CK before Immunotherapy	1354	(270-4597)	6
CK after Immunotherapy	270	(110-1009)	4
Maximum CK, IU/L	2500	(1087-3527)	9
Nadir CD4 count	168	(145-427)	8
CD4 count at IBM diagnosis	833	(355-968)	8
Vital capacity at IBM diagnosis visit, Litres	2.2	(2-2.2)	7

Abbreviations: No., number; IQR, interquartile range; ART, antiretroviral therapy; PM, polymyositis; IBM, inclusion body myositis; CK, creatine kinase; FRS, Functional Rating Scale

[a] Continuous variables are presented as median (IQR), and categorical variables as No. (%)

All the patients were female with a median age of 50 years at IBM diagnosis with two of them younger than 45 years and not meeting the conventional criteria for non-HIV

sporadic IBM. However most patients (seven) had symptoms onset before 40 years and only one patient after 45 years. The patients generally presented with moderately advanced HIV-infection with a median nadir CD4 count of 168 cells per microliter. Furthermore, six patients were treated for pulmonary tuberculosis at or after HIV diagnosis. However, once ART was initiated, none of our patients had uncontrolled viral load during the follow up time.

From the folder review and retrospective patient recall, proximal lower limb weakness was the initial complaint of all of our patients that started at a median age of 36 years. Only one patient also reported hand grip weakness as an additional initial symptom. None of the patients were noted to have a typical dermatomyositis rash either prior to presentation, or during follow-up. The median duration from HIV diagnosis to symptom onset was 18 months and ranged between 3 and 49 months.

ART was initiated after a median period of 1.5 (0-62) months from HIV diagnosis. All the patients had been treated with at least two ART regimens since HIV diagnosis due to change in government ART programme policies. 44.4% were on a tenofovir, lamivudine and dolutegravir (TLD) regimen at the last follow up visit. One patient was exposed to a statin but had no features of IMNM clinically or histopathologically. One patient was exposed to zidovudine for an unknown number of years prior to symptom onset that was eventually stopped.

The median maximum CK recorded was 2500 IU/L. None of the patient had a recorded CK of more than 15 times the upper limit of normal. The interval between symptom onset to IBM diagnosis was 11 years (range: 6-15) and the interval between PM diagnosis and IBM diagnosis was 9 years (range: 3-14).

At the “neurology” visit when patient’s diagnosis was changed to HIV-IBM, two had been referred by rheumatologist for treatment refractory PM, one was referred by a physician as PM with an underlying peripheral neuropathy and without immunotherapy, one patient presented late to a private neurologist and was referred as PM with atypical features. The remaining five patients had a diagnosis of PM made by Groote Schuur Hospital (GSH) neurology.

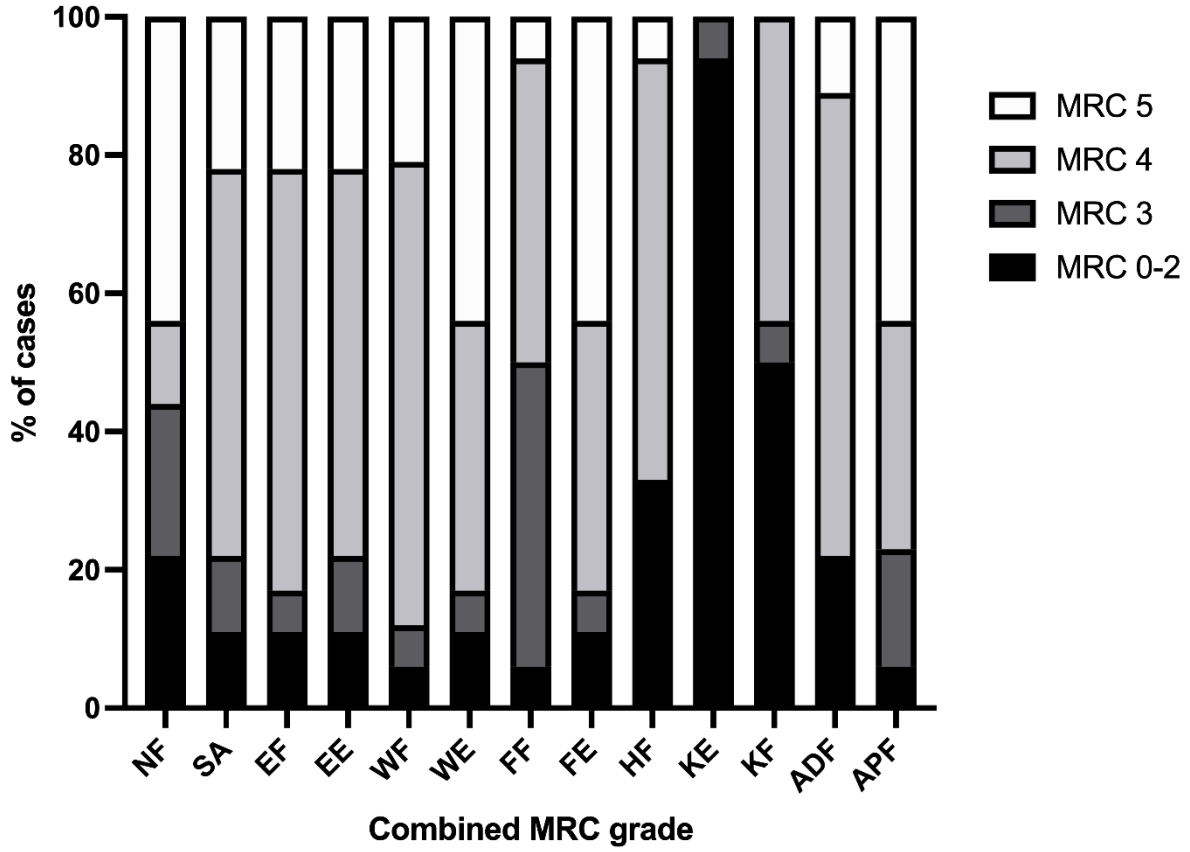
Audit of Examination Findings as written in hospital notes

All nine patients were examined after a median symptom duration of 12 years. After about 1.5 years of follow up, two of six patients in whom data were available already satisfied the ENMC 2011 clinical criteria for IBM; one with quadriceps weakness more than hip flexors weakness and the other with both finger flexors weakness more than shoulder abductors weakness and quadriceps weakness more than hip flexors weakness. After three years of follow up, an additional patient (3 of 6) satisfied the clinical ENMC 2011 IBM criteria and after five years a total number of four patients (4 of 6) satisfied the clinical ENMC 2011 IBM criteria.

Figure 1 shows a histogram depicting the severity of muscle weakness according to Medical Research Council (MRC) scores of distinct muscle groups in all nine cases at final IBM visit which was performed after a median of 12 years. Of the most severely affected muscles in the lower limbs with MRC grades of 0-2 (out of 5), the knee extensors were most frequent (≥ 90% of cases), followed by knee flexors (≥ 50%) and hip flexors (≥ 30%). In the upper limbs, the finger flexors were the most involved with moderately weak muscles in 50% and mildly weak muscles in another approximately 45%. Normal finger flexor power was noted in 5 % cases as one patient had normal finger flexor power on the right side but moderately weak finger flexor on the left side indicating asymmetric weakness in the hands. More than 80% of patients had mild to severe weakness in other upper limb muscles as well. Of note, ≥ 20% of patients had severe weakness of neck flexors and ankle dorsiflexors.

At the final visit most patients were substantially disabled and only two were able to mobilize independently. Four (44.4 %) patients reported mild dysphagia at IBM diagnosis visit with a median severity score of 3/10 on a numerical scale but none reported choking. The median IBM Functional Rating Scale at IBM diagnosis visit was 22 ranging between 9 and 24.

Figure 1: Medical Research Council (MRC) scores of distinct muscle groups at final visit



Legend: We pooled the scores of all nine patients, included both sides, and represent that as percentage.

Abbreviations: %,Percentage; MRC, Medical Research Council (Scale for Muscle Strength); NF, Neck Flexion; SA- Shoulder Adduction; EF, Elbow Flexion; EE, Elbow Extension; WF, Wrist Flexion; WE, Wrist Extension; FF, Finger Flexion; FE, Finger Extension; HF, Hip Flexion; KE, Knee Extension; KF, Knee Flexion; ADF, Ankle Dorsiflexion; APF, Ankle Plantar Flexion

Hand Grip dynamometer (HGD) testing was performed in six patients at the final IBM visit. The median HGD values for the left and right hand on last visit were 9.9 kg (58% drop compared to expected for age group) and 10.8 kg (54% drop compared to expected for age group), respectively. Six of eight patients could not perform the TUG test at last visit as they were unable to stand up from a sitting position. The other two patients took 68 and 36 seconds to perform the test respectively.

Exposure to immune therapies prior to IBM diagnosis

Seven of nine patients received immunotherapy. Two patients did not receive immunotherapy as the diagnosis was unclear with one of them referred to us with a diagnosis of PM with underlying neuropathy after four years of symptoms and the other presented after thirteen years to a private neurologist before referral to GSH neurology for work up. Table 8 shows the different drugs prescribed to our HIV-IBM patients by clinicians prior to the diagnosis of IBM and exposure time for each drug.

All patients who received any form of immunosuppressive therapy received prednisone for a median time of 137 months (range: 24-180). The most common other immunosuppressive agents used were azathioprine and methotrexate with a median exposure time of 16 and 15 months respectively. The median number of immunosuppressants used by patients who received any form of immunotherapy (n=7) was four. Four patients reported subjective clinical improvement following immunotherapy that was relatively short-lived (median duration: 22 months [(range: 8-53)]) and then became resistant to treatment with worsening limb weakness. Three of seven patients showed objective improvement with prednisone and methotrexate for the first two years of treatment. Three patients reported no response to immunotherapy.

Table 8: The different drugs prescribed to our HIV-IBM patients by clinicians prior to the diagnosis of IBM and exposure time for each drug

	All Patients (n=9)		
	Median (IQR) or No. (%)[a]		No. with Data Available
Management prior to IBM diagnosis			
Received immunotherapy	7	(78)	9
No. of immunosuppressants per patient	4	(3-6)	7
Immunosuppressive agents exposure, months	137	(24-180)	7
Received prednisone	7	(78)	9
Prednisone exposure, months	137	(24-180)	7
Received azathioprine	5	(56)	9
Azathioprine exposure, months	16	(8-46)	5
Received methotrexate	6	(67)	9
Methotrexate exposure, months	15	(12-72)	6
Received cyclophosphamide	3	(33)	9
Cyclophosphamide exposure, months	4	(3-6)	3
Received rituximab	3	(33)	9
Rituximab exposure, months*	15	(12-24)	3
Received Cyclosporin	2	(22)	9
Cyclosporin Exposure, months	14	(11-18)	2
Received MMF	2	(22)	9
MMF Exposure, months	54	(40-67)	2

Abbreviations: No., number; IQR, interquartile range; MMF, mycophenolate mofetil

*Rituximab infusions were 6-monthly. So patients received at least 2-4 infusions.

[a] Continuous variables are presented as median (IQR), and categorical variables as No. (%)

Auditing the original muscle biopsy reports

All nine patients had muscle biopsies between 12 and 35 months after onset of symptoms. The muscle biopsies were all processed and reported at the Red Cross Children's hospital pathology laboratory, but at different time periods. Five of our patients had two muscle biopsies; the second biopsy was performed between 3 and 12 years after the first one. Table 8 shows the summary of an audit of muscle biopsy findings of GSH HIV-IBM patients.

The most important findings were that all patients had evidence of inflammatory infiltrate, but 8 of 9 had evidence of chronicity with increased connective tissue (CT).

Only one patient did not show increased CT in a biopsy done 21 months after symptom onset. The increase in CT was graded in some reports with 3 of 9 first muscle biopsy (FMB) samples reported as mild and 2 of 4 second muscle biopsy (SMB) samples reported as marked. Variation of myofibres were noted in all muscle biopsies with four FMB samples (44%) reported as marked and three SMB samples (60%) reported as mild whereas atrophic fibres were noted in 67% of FMB samples and in all SMB samples. Two SMB samples showed Oil red O positivity indicating increase in sarcoplasmic lipid.

An increase in MHC 1 expression and mitochondrial abnormalities (evidenced by COX – /SDH + fibre staining patterns) were noted in all four patients in whom immunohistochemical staining and combined SDH and COX staining were performed, although this was not routinely performed at the time. The combined SDH and COX staining were performed on four first biopsy samples and one second biopsy sample. MHC Class 1 immunohistochemical stain were performed on 3 of 9 FMB (33%) and 1 of 5 SMB (20%). They all showed 100% MHC class 1 positivity. None of the patients were mentioned to have rimmed vacuoles or 15-18nm filaments in their muscle biopsy. P62/Tar DNA binding protein 43 (TDP43) staining was not available and therefore protein aggregates/inclusions were not looked for.

Electron microscopy was performed on 5 of 9 FMB samples (56%) and 2 of 5 SMB samples (40%). Moreover on electron microscopy, it is to be noted that mitochondrial abnormalities were reported in 1of 5 FMB samples (20%) and 1 of 2 SMB samples (50%). Only 17% of FMB samples showed Red Ragged Fibres on Gomori staining which is also an indicator of mitochondrial abnormalities.

Table 9: A summary of muscle biopsy findings of our HIV-IBM patients

	All Patients (n=9)					
	No. (%)[a]				No. with Data Available	
Muscle biopsy histological findings	**FMB**		**SMB**		**FMB**	**SMB**
	No.	**(%)**	**No.**	**(%)**		
Variation of myofiber size	9	(100)	4	(100)	9	4
Atrophic fibres	6	(67)	5	(100)	9	5
Increase in internal nuclei	6	(67)	2	(50)	9	4
Necrotizing /Degenerating fibres	8	(89)	3	(75)	9	4
Regenerating fibres	6	(75)	2	(50)	8	4
Increase endomysial CT	8	(89)	3	(75)	9	4
Inflammatory infiltrate	9	(100)	4	(100)	9	4
Gomori-RRF	1	(17)	0		6	3
NADH-focal target fibres	3	(50)	0		6	2
MYO S&F; ATPase (Atrophic type 1 & 2 fibres)	2	(33)	0		6	2
MYO S&F; ATPase (Type 1/ 2 fibre predominance)	2/0	(33)/0	0		6	2
MHC 1	3	(100)	1	(100)	3	1
COX –ve /SDH +ve	4	(100)	1	(100)	4	1
PAS abnormalities	0		0		4	1
Oil red O	0		2	(100)	4	2
Rimmed vacuoles	0		0		9	5

Abbreviations: No.,number; IQR, interquartile range; FMB, first muscle biopsy; SMB, second muscle biopsy; CT, connective tissue; RRF, red ragged fibre; MYO-ATPase, myosin ATPase enzyme; MHC, major histocompatibility; COX, cytochrome C oxidase; SDH, succinate dehydrogenase; PAS, Periodic acid-schiff

[a] Categorical variables as No. (%)

Observations at the visit when the clinical diagnosis was altered to HIV-IBM

We collated the neurological examination findings of either the neurology registrar (BBR) or consultant (JH) at the "IBM" visit. At this visit the patient underwent an examination, the IBM-FRS was completed and hand grip measurements were recorded. Table 9 refers to the percentage of our case series satisfying the ENMC IBM Research Diagnostic Criteria 2011 at final visit; five patients could be categorized as clinically defined IBM and four were defined as clinically probable IBM. None of them satisfied the clinicopathological criteria for IBM as P62/TDP43 staining to detect protein aggregates was not performed in our laboratory and rimmed vacuoles were not detected in any patients but it is unclear whether it were routinely sought for as it

was not mentioned in the biopsy reports. At final visit, 6 (67%) patients satisfied the mandatory criteria for non-HIV IBM and 5 (56%) patients satisfied the clinical criteria i.e quadriceps weakness > hip flexors weakness and finger flexors weakness > shoulder abductors weakness.

Table 10 shows the percentage of our case series satisfying the ENMC IBM Research Diagnostic Criteria 2011 [17] at final visit after a median 12 years of symptoms.

PATIENT CHARACTERISTICS	All Patients (n=9)		
	No.	(%)[a]	No. with Data Available
Age > 45 years	6	(67)	9
Duration of symptoms > 12 months	9	(100)	9
CK ≤15 times upper limit of normal	9	(100)	9
Mandatory criteria for non-HIV IBM*	6	(67)	9
Quadriceps weakness > Hip flexors weakness	6	(67)	9
Finger flexors > shoulder abductors weakness	7	(78)	9
Quadriceps weakness > Hip flexors weakness and Finger flexors > shoulder abductors weakness	5	(56)	9
Endomysial Inflammatory infiltrates	9	(100)	9
Rimmed Vacuoles	0		9
Protein accumulation	-		0
Upregulation of MHC I	4	(44)	9
Mitochondrial abnormalities	5	(100)	5
Clinicopathologically defined IBM	0		9
Clinically defined IBM	5	(56)	9
Probable IBM	4	(44)	9

*Mandatory Criteria for IBM: Age of onset ≥ 45 years, duration of symptoms ≥ 12 months, serum creatine kinase level ≤ 15X upper limit of normal

Abbreviations: No., number; IBM, inclusion body myositis

[a] categorical variables as No. (%)

Figure 2 and 3 show important signs and clues in our patients that could help in early detection and diagnosis of IBM

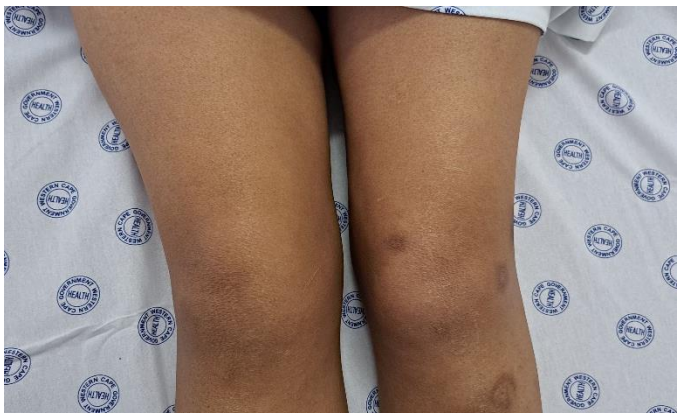


Figure 2 shows asymmetric wasting of bilateral quadriceps

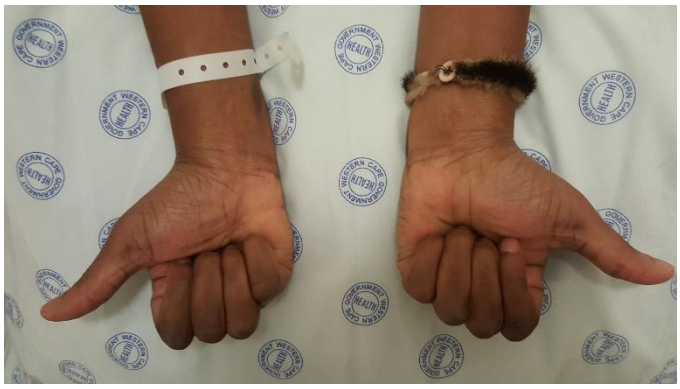


Figure 3 shows inability of patient to bury left hand finger nail completely while making a close fist

CHAPTER 6: DISCUSSION AND CONCLUSION

Here we describe nine patients in whom the diagnosis of HIV-PM was later changed to HIV-IBM based on clinical findings after a median disease duration of 12 years. Even though the median time from HIV-PM diagnosis to HIV-IBM diagnosis was nine years, two patients after a follow up time of 1.5 years already satisfied the ENMC 2011 clinical criteria for IBM [21] and were subjected to many years of unnecessary immune treatment. Delayed recognition of this progression from HIV-PM to HIV-IBM probably related to poor awareness of this entity.

All the patients in our cohort were female compared to previous literature in which the majority were male. Three of our HIV-IBM patients were younger than the age criteria for non-HIV sporadic IBM at the IBM visit. Similar findings were noted by Couture P [22] et al. and Lloyd et al. [30] As all these patients had otherwise typical IBM features but were younger, the age criteria of ENMC 2011 may not be applicable to HIV-IBM patients. All the nine patients described in this study fulfilled the old Bohan and Peter criteria for PM [14] at their very first visit.

Another important point of my study is that out of the seven patients who received immunotherapy, only four subjectively and objectively responded to treatment for a short time (median period: 22 months [(range: 8-53)]). Adding or changing immunosuppressive agents might expose the patient to unnecessary side effects like nausea, vomiting, diarrhoea, diabetes mellitus, osteoporosis, peptic ulcer, bone marrow suppression, hepatotoxicity, nephrotoxicity and infections. [42] Treatment refractoriness is an important red flag here that should prompt clinicians to look for signs suggestive of IBM.

The CK level of a HIV-positive myositis patient is roughly 2-4 times the normal and rarely exceeds 1200 IU/L. [43] However, the maximum CK level in this cohort was 2500 IU/L with six out of nine patients having levels above 1200IU/L. A relatively high CK but less than 15 times the upper limit of normal is a clue for this disease progression.

The ENMC 2011 biopsy diagnostic criteria of IBM does not include mitochondrial abnormalities but it is reported in the literature that it has 100% sensitivity and 73% specificity for IBM in the absence of rimmed vacuoles. [19] In our study all the patients who had COX/SDH staining showed marked COX negative and SDH positive fibres which are indicators of mitochondrial abnormalities. However, not all biopsies had this

analysis. Some authors concluded that non-specific myositis with mitochondrial pathology may be considered as a possible early form of IBM. [15] We recommend performing COX/SDH staining on all inflammatory myopathy muscle biopsy samples for early recognition of IBM.

The main limitations of this study were its retrospective nature (i.e. comprehensive clinical and laboratory findings were incomplete), the small number of patients in this case series and inability to perform P62/TDP 43 staining to detect protein aggregates on muscle biopsy samples and anti 5 nucleotidase 1A antibody testing to support the diagnosis of IBM due to resource limitation. Table 11 shows the clues to earlier diagnosis of HIV IBM.

Table 11

History:
Patient satisfying ENMC 2011 clinical criteria for IBM except for age.
Treatment refractory with at least two immunosuppressive agents after two years since PM diagnosis.
Clinical Examination:
Asymmetric atrophy of the quadriceps and medial forearm flexors muscles and finger flexor weakness which is disproportionately greater than that of the hip flexors and shoulder abductors, respectively.
Investigations:
A relatively high CK but less than 15 times the upper limit of normal.
Muscle biopsy: suggest testing for COX/SDH staining and electron microscopy to detect mitochondrial abnormalities and to look for increase in MHC 1 expression.

Abbreviations: ENMC, European Neuromuscular Centre; IBM, inclusion body myositis; PM, polymyositis; CK, Creatine kinase; MHC, major histocompatibility; COX, cytochrome C oxidase; SDH, succinate dehydrogenase

Conclusion

The co-occurrence of HIV infection and IBM is rare but not coincidental. From these results, we identified and described the earliest clinical and histopathological ‘Red Flags’ of this refractory HIV-IBM group according to the international criteria for diagnosing IBM. This study will alert treating clinicians (neurologists and rheumatologist) to be mindful of this clinical entity to enable more cost-effective and safe management of IBM in HIV-positive patients.

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APPENDIX 1

Inclusion Body Myositis Functional Rating Scale

1. **Swallowing**
   - 4 Normal
   - 3 Early eating problems — occasional choking
   - 2 Dietary consistency changes
   - 1 Frequent choking
   - 0 Needs tube feeding

2. **Handwriting (with dominant hand prior to IBM onset)**
   - 4 Normal
   - 3 Slow or sloppy; all words are legible
   - 2 Not all words are legible
   - 1 Able to grip pen but unable to write
   - 0 Unable to grip pen

3. **Cutting Food and Handling Utensils**
   - 4 Normal
   - 3 Somewhat slow and clumsy, but no help needed
   - 2 Can cut most foods, although clumsy and slow; some help needed
   - 1 Food must be cut by someone, but can still feed slowly
   - 0 Needs to be fed

4. **Fine Motor Tasks (Opening doors, using keys, picking up small objects**
   - 4 Independent
   - 3 Slow or clumsy in completing task
   - 2 Independent but requires modified techniques or assistive devices
   - 1 Frequently requires assistance from caregiver
   - 0 Unable

5. **Dressing**
   - 4 Normal
   - 3 Independent but with increased effort or decreased efficiency
   - 2 Independent but requires assistive devices or modified techniques (Velcro, snaps, shirts without buttons, etc.)
   - 1 Requires assistance from caregiver for some items
   - 0 Total dependence

6. **Hygiene (Bathing and Toileting)**
   - 4 Normal
   - 3 Independent but with increased effort or decreased activity
   - 2 Independent but requires use of assistive devices (shower chair, raised toilet seat, etc.)
   - 1 Requires occasional assistance from caregiver
   - 0 Completely dependent

7. **Turning in Bed and Adjusting Covers**
   - 4 Normal
   - 3 Somewhat slow and clumsy but no help needed
   - 2 Can turn alone or adjust sheets, but with great difficulty
   - 1 Can initiate, but not turn or adjust sheets alone
   - 0 Unable or requires total assistance

8. **Sit to Stand**
   - 4 Independent (without use of arms)
   - 3 Performs with substitute motions (leaning forward, rocking) but without use of arms
   - 2 Requires use of arms
   - 1 Requires assistance from a device or person
   - 0 Unable to stand

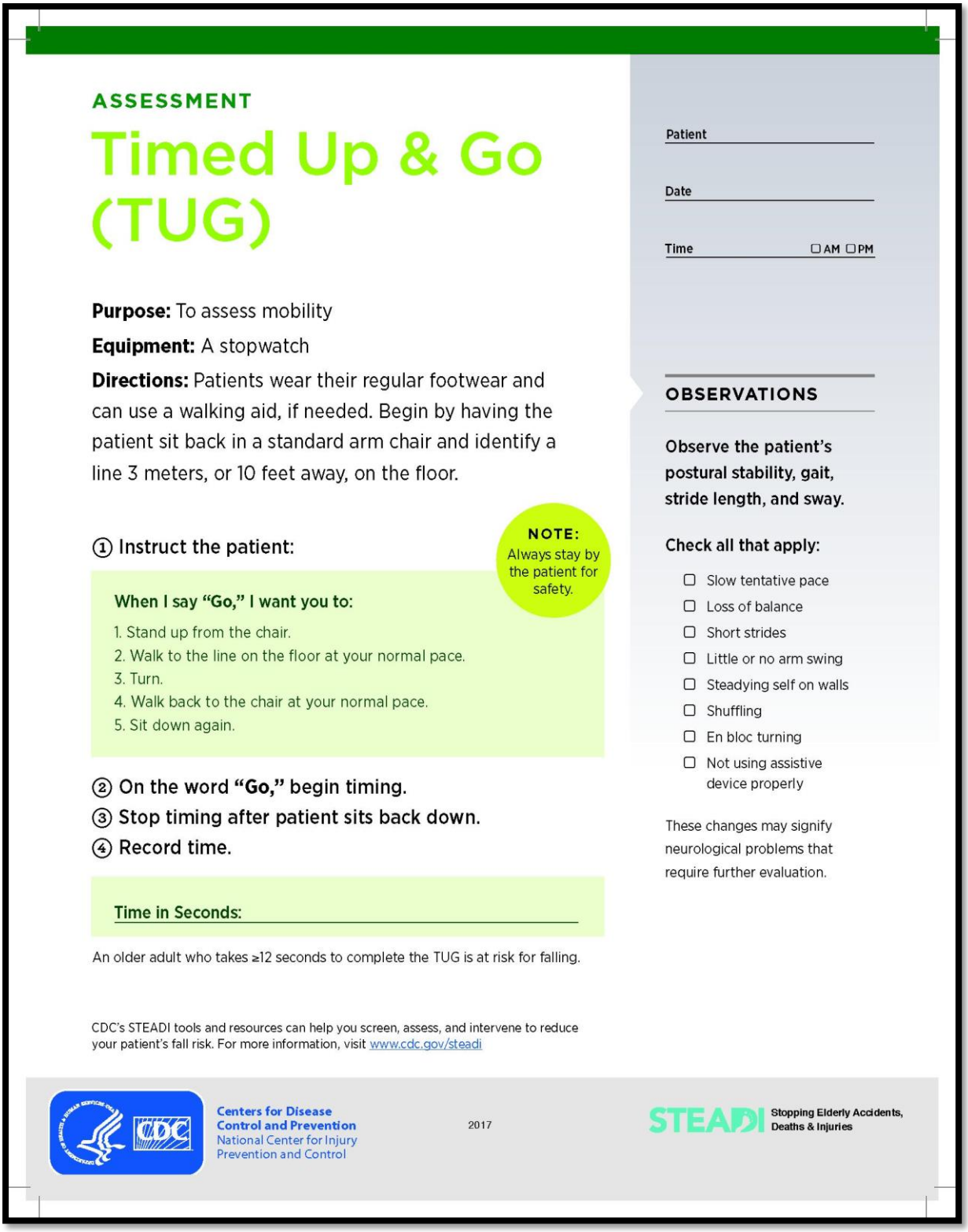
9. **Walking**
   - 4 Normal
   - 3 Slow or mild unsteadiness
   - 2 Intermittent use of an assistive device (ankle-foot orthosis, cane, walker)
   - 1 Dependent on assistive device
   - 0 Wheelchair dependent

10. **Climbing Stairs**
    - 4 Normal
    - 3 Slow with hesitation or increased effort; uses hand rail intermittently
    - 2 Dependent on hand rail
    - 1 Dependent on hand rail and additional support (cane or person)
    - 0 Cannot climb stairs

Add the individual scores to yield the total score. Maximum total score is 40.

Jackson, C., Barohn, R., Gronseth, G., Pandya, S., & Herbelin, L. (2008). Inclusion body myositis functional rating scale: A reliable and valid measure of disease severity. *Muscle & Nerve, 37*(4), 473-476.

APPENDIX 2



ASSESSMENT

Timed Up & Go (TUG)

Patient _____

Date _____

Time _____ ☐ AM ☐ PM

Purpose: To assess mobility

Equipment: A stopwatch

Directions: Patients wear their regular footwear and can use a walking aid, if needed. Begin by having the patient sit back in a standard arm chair and identify a line 3 meters, or 10 feet away, on the floor.

NOTE: Always stay by the patient for safety.

① **Instruct the patient:**

When I say "Go," I want you to:

1. Stand up from the chair.
2. Walk to the line on the floor at your normal pace.
3. Turn.
4. Walk back to the chair at your normal pace.
5. Sit down again.

② **On the word "Go," begin timing.**

③ **Stop timing after patient sits back down.**

④ **Record time.**

Time in Seconds: _____

An older adult who takes ≥12 seconds to complete the TUG is at risk for falling.

CDC's STEADI tools and resources can help you screen, assess, and intervene to reduce your patient's fall risk. For more information, visit www.cdc.gov/steadi

OBSERVATIONS

Observe the patient's postural stability, gait, stride length, and sway.

Check all that apply:

- ☐ Slow tentative pace
- ☐ Loss of balance
- ☐ Short strides
- ☐ Little or no arm swing
- ☐ Steadying self on walls
- ☐ Shuffling
- ☐ En bloc turning
- ☐ Not using assistive device properly

These changes may signify neurological problems that require further evaluation.

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

2017

STEADI Stopping Elderly Accidents, Deaths & Injuries

UNIVERSITY OF CAPE TOWN
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20 June 2023

HREC REF: 397/2023

Prof J Heckmann
Division of Neurology
E8 NGSH
Email: Jeanine.heckmann@uct.ac.za
Student: b.basantrai@yahoo.com

Dear Prof Heckmann

PROJECT TITLE: HIV-POLYMYOSITIS PROGRESSING TO INCLUSION BODY MYOSITIS: CLUES TO EARLIER DIAGNOSIS-
(MMED CANDIDATE-DR BHUVANESHLAL RAI)

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

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

Approval is granted for one year until the 30 June 2024.

You are required to submit a progress report form, using the standardised Annual Report Form (FHS016) 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)

The HREC acknowledge that the student: Dr Bhuvaneshlal Rai will also be involved in this study.

Please quote HREC REF 397/2023 in all your correspondence.

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

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

Signed by candidate

M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research

Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.