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A 15 -Year Review of Multiple Myeloma in HIV-1 Seropositive Patients at Chris Hani Baragwanath Academic Hospital

Baxter, Jayson McNeil

2024

University of the Witwatersrand, Johannesburg

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Baxter, Jayson McNeil. (2024). A 15 -Year Review of Multiple Myeloma in HIV-1 Seropositive Patients at Chris Hani Baragwanath Academic Hospital [Master's dissertation, University of the Witwatersrand, Johannesburg]. WireDSpace.https://hdl.handle.net/10539/42356

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A 15 -Year Review of Multiple Myeloma in HIV-1 Seropositive Patients at Chris Hani Baragwanath Academic Hospital

Jayson McNeil Baxter
Student number: 0702132K

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine (Internal Medicine)

Johannesburg, 2024

ETHICS COMMITTEE APPROVAL

This study was approved by the Human Research Ethics Committee (HREC) (Medical), University of the Witwatersrand: Clearance certificate no. M201170 (see Appendix A). Approval was later granted by the HREC to extend the study inclusion period by 12 months (see Appendix B).

DECLARATION

I declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine (in the specialty of Internal Medicine) to the University of the Witwatersrand. This research report has not been submitted before for any degree or examination at this or any other University.

I am aware that plagiarism is a serious offense and is tantamount to fraud. I have not attempted to pass off another author or entity's work, words or ideas as my own. I have not misrepresented my findings as novel or original if there is an existing source. All work has been referenced appropriately.



(Signature of candidate)

24th day of January 2024, at CHBAH

DEDICATION

To my partner, family and mentors

ACKNOWLEDGEMENTS

I would like to thank my supervisors, Professor Patel and Dr Lakha, for their patience, support and guidance throughout this research process.

I would also like to thank and acknowledge the following persons/individuals for their assistance and contributions in different ways:

1. The Clinical Haematology Unit (team) and the Department of Medicine at Chris Hani Baragwanath Academic Hospital (including the medical, nursing, and allied staff),
2. All the patients whose data was used in the study,
3. The Clinical Haematology Unit secretary, Mrs Gwendoline Stander, for her kind assistance at all times, and
4. The statisticians, for kindly assisting with the statistical analysis of the results in the study.

ABSTRACT

Background:

Multiple Myeloma (MM) is a haematological malignancy characterized by the malignant proliferation of plasma cells in the bone marrow and manifesting with skeletal related events as the clinical and radiological hallmark of the disease.

The incidence of MM varies substantially across the different continents, with intermediate rates being encountered in Africa. MM occurs more commonly in people of Afro-Caribbean descent, with the incidence being 2-fold higher in African Americans compared to Caucasians. In South Africa, prior to the advent of and impact of HIV, MM was the most common haematological malignancy in adults. However, since 2002, Non-Hodgkin Lymphoma (NHL) has superseded MM, with MM being the second most common haematological malignancy encountered in adults, currently.

At Chris Hani Baragwanath Academic Hospital (CHBAH), MM has been a stable disease since the 1970's, with a noticeable increase in numbers since 2016. MM is characteristically a disease of middle-aged and elderly individuals. In the Western world, ninety-eight percent of cases occur over the age of 40 years with a peak in incidence in the seventh decade. The median age at diagnosis is 66 years. However, in Africa, the disease presents at a younger median age (approximately 5-10 years younger), with 7% of the patients being under the age of 40 years.

In 2020, globally there were 36 million adults with HIV-1 of which 67% were living in sub-Saharan Africa. Women accounted for 63% of all new HIV-1 infections, compared to men with 37%. South Africa has the highest number of HIV-1 sero-positive individuals in the world and is home to approximately 8 million people living with HIV (PLWH). In South Africa, HIV has reached epidemic proportions and is impacting on a number of haematological malignancies, including MM.

This study was undertaken to better characterize and describe the demographics, clinical, laboratory and radiological findings of patients presenting with HIV-1 sero-positivity and concomitant MM in our patient population. In addition, it describes the therapy, response to therapy, outcome and survival of the patients with this association.

b. Patients and Methods:

This is a retrospective study of all adult patients with a confirmed diagnosis of MM, together with HIV-1 sero-positivity, seen at the Clinical Haematology Unit, Department of Medicine, from January 2006 to December 2020 (15 years). Demographic, clinical, radiological and therapeutic data was retrieved from the patient files and laboratory data from the NHLS data

base. Data was processed in Microsoft Excel and the appropriate statistical software was used to analyse the results. Descriptive analysis was conducted through the computation of frequency tables for categorical variables and appropriate measures of central tendency, i.e., mean, ± SD/median and (IQR), for continuous variables. Kaplan-Meier survival curves were plotted to determine the survival probability of the patients based on the clinical, laboratory and treatment characteristics.

c. Results and Discussion:

During the study period (01/01/2006 to 31/12/2020 – 15 years), a total of 601 patients were diagnosed with MM. 84 patients were HIV-1 seropositive (14%). Of these 84 patients, 14 were excluded. A total of 70 evaluable HIV-1 seropositive patients were included in this study (12%). Of these 70 patients, there were 42 females and 28 males with a female to male ratio of 1.5:1. The mean age for females was 49.9 years (range 31-77 years), and males was 50.6 years (range 36-73 years), while the mean age for the whole group was 50.2 years (range 31-77years). All the patients in the study were of Black African ethnicity, in keeping with the demographic of CHBAH, where >90% of the patients admitted to the hospital are of Black African ethnicity. The pertinent findings in this study were the following:

1. An increase in the number of MM patients from 165 (2006-2010) and 168 (2011-2015), to 268 (2016-2020), in the latter five years of the study. A corresponding increase in HIV seropositivity of 10.9% (2006-2010) and 10.1% (2011-2015), to 18.3% (2016-2020) in the latter 5 years of the study, with a background seroprevalence in Gauteng of 14.9% (2005) to 14.4% (2008) and 18.8% (2012) to 18.7% (2017),
2. A younger mean age of 50 years, with a female predominance of 1.5:1,
3. More than half the patients (54.7%) had an ECOG PS ≥2,
4. Bone pain and anaemia were the dominant clinical features,
5. A higher proportion of cytopenias, including leucopenia, neutropenia and thrombocytopenia was noted in the study population compared to other studies done locally at CHBAH on MM.
6. Plasmacytomas were evident clinically in 29% of patients and radiologically in 52% of patients.
7. Biochemical features of note were: hypercalcaemia in 56% of patients, renal dysfunction in 33% of patients, hypoalbuminaemia in 65% of patients and an elevated B2M level in 96.3% of the patients. The mean CD4 count was 367 cells/ul, with a range of 23-964 cells/ul. Approximately a quarter of the patients (26.1%) had a CD4 count <200 cells/ul,
8. IgG isotype (74%) was the most common subtype of MM,

9. Lytic lesions were found in up to 77% of the patients on CT scan, with vertebral compression fractures being present in 77% of patients on MRI.

10. Most patients had advanced stage of disease, with DS stage III in 92% of the patients and ISS stage III in 70% of the patients.

11. Specific therapy in the form of chemotherapy (different combinations of cytotoxics, corticosteroids and immunomodulatory agents such as thalidomide etc.) was administered to 76% of the patients. Furthermore, 34% had radiotherapy and only 6% had an ASCT,

12. Despite the use of cART and specific therapy, the overall outcome was poor, with a median survival of 5.64 months (Interquartile range 0.82-19.24 months),

13. Survival was statistically significantly better in those who received chemotherapy and/or radiotherapy compared to those who received supportive care only ($p=<0.001$) and those who had ISS stage I and II disease, compared to ISS stage III disease ($p=0.006$), and

14. Although survival was better in those who had a higher CD4 count (≥200 cells/ul versus <200 cells/ul) ($p=0.081$), and those who achieved at least a PR versus <PR ($p=0.108$), these two parameters were not statistically significantly different.

d: Conclusions and Future recommendations:

Although chronic antigenic stimulation and immunodeficiency in HIV-1 sero-positive individuals may contribute to an increased risk of MM, it is unclear whether the association between the two diseases in our patients, is causal or coincidental. Nevertheless, what is apparent is that this association is increasing (18% in the latter five years of the study). As such, we need to create awareness of this, so that the patients can be recognized, diagnosed and treated timeously, in order to improve the prognosis and outcomes of the patients.

It is clear from this study, that MM in association with HIV-1 sero-positivity presents in younger individuals, with a female predominance, with typical and characteristic features of bone pain, anaemia, lytic bone lesions, vertebral compression fractures, hypercalcaemia, renal dysfunction, as well as more frequent extramedullary manifestations such as plasmacytomas, predominance of an IgG isotype, advanced stage disease and inferior outcomes.

Future recommendations should include:

Continued efforts to prevent, minimize and lessen the burden of HIV, together with early initiation of antiretroviral therapy, recognition of, and aggressive and optimal management of complications of the disease.

Education with regard to the key clinical manifestations of MM, early suspicion of the diagnosis and timeous referral to a tertiary or specialized centre, so that treatment can be initiated as soon as possible.

Appropriate follow up of the patients to assess response to treatment and to detect early relapse or progression of the disease.

Efforts to improve accessibility of ‘state of the art’ and novel therapies for public sector patients.

Increase the number of patients who require an ASCT, as part of consolidation treatment.

Furthermore, prospective, multicentre studies need to be undertaken to optimally manage HIV-1 sero-positivity in association with MM. In principle, these patients should be offered the same treatment options as HIV-1 sero-negative individuals, with the proviso that every attempt is made to achieve optimal virological suppression and immune reconstitution.

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LIST OF ABBREVIATIONS

ADH:	Anti-diuretic hormone
AIDP:	Acute inflammatory demyelinating polyneuropathy
AIDS:	Acquired immunodeficiency syndrome
AL:	Light chain amyloidosis
ALP:	Alkaline phosphatase
APOL1:	Apolipoprotein L1
ASCT:	Autologous stem cell transplant/transplantation
ATN:	Acute tubular necrosis
B2M:	Beta-2-microglobulin
BRCA 1:	Breast cancer gene 1
BRCA 2:	Breast cancer gene 2
CAR T-cells:	Chimeric antigen receptor T-cells
cART:	Combination antiretroviral therapy
CC:	Chemokine
CCR:	Chemokine receptor
CCR5:	Chemokine receptor type 5
CD4:	Cluster of differentiation 4
CD8:	Cluster of differentiation 8
CD14:	Cluster of differentiation 14
CD163:	Cluster of differentiation 163
CDC:	Centres for Disease Control
CDKN2A:	Cyclin-dependent kinase inhibitor 2A
CDKN2C:	Cyclin-dependent kinase inhibitor 2C
CHBAH:	Chris Hani Baragwanath Academic Hospital
CI:	Confidence Interval
CIDP:	Chronic inflammatory demyelinating polyneuropathy
CR:	Complete response
CTL:	Cytotoxic T lymphocyte
CXCR4:	C-X-C chemokine receptor type 4
DILS:	Diffuse infiltrative lymphomatosis syndrome
DKK1:	Dickkopf1
DS:	Durie-Salmon stage
DTG:	Dolutegravir

DPd:	Daratumumab, Pomalidomide, Dexamethasone
DRd:	Daratumumab, Lenalidomide (Revlimid), Dexamethasone
DVd:	Daratumumab, Bortezomib (Velcade), Dexamethasone
EBV:	Epstein Barr Virus
ECOG:	Eastern Cooperative Oncology Group
ELISA:	Enzyme linked immunosorbent assay
EPO:	Erythropoietin
ERd:	Elotuzumab, Lenalidomide (Revlimid), Dexamethasone
EPd:	Elotuzumab, Pomalidomide, Dexamethasone
FGFR3:	Fibroblast growth factor receptor 3
FLC:	Free light chain
FSGS:	Focal segmental glomerulosclerosis
FTC:	Emtricitabine
GCSF:	Granulocyte colony stimulating factor
HAART:	Highly active antiretroviral therapy
Hb:	Haemoglobin
HCDD:	Heavy chain deposition disease
HHV-8:	Human herpes virus - 8
HIV:	Human immunodeficiency virus
HIVAN:	HIV associated nephropathy
HIV-ATN:	Antiretroviral toxic neuropathy
HIV-PN:	HIV-associated distal peripheral sensory neuropathy
HLAB18:	Human leukocyte antigen B18
HLAB35:	Human leukocyte antigen B35
HLAB5701:	Human leukocyte antigen B5701
HREC:	Human Research Ethics Committee
IFN-a:	Interferon alpha
IFN-g:	Interferon-gamma
Ig:	Immunoglobulin
IL-1:	Interleukin1
IL-1b:	Interleukin-1 beta
IL-3:	Interleukin -3
IL-6:	Interleukin-6
IL-8:	Interleukin-8

IMWG:	International Myeloma Working Group
IQR:	Interquartile range
IRd:	Ixazomib, Lenalidomide (Revlimid), Dexamethasone
IRIS:	Immune reconstitution inflammatory syndrome
Isa-Pd:	Isatuximab, Pomalidomide, Dexamethasone
ISS:	International staging system
KM:	Kaplan-Meier
KRAS:	Kirsten rat sarcoma virus–RAS
KRd:	Kyprolis, Lenalidomide (Revlimid), Dexamethasone
KS:	Kaposi's sarcoma
LCDD:	Light chain deposition disease
LDH:	Lactate dehydrogenase
LHCDD:	Light and heavy chain deposition disease
MAF:	Musculoaponeurotic fibrosarcoma
MAPK:	Mitogen activated protein kinase
MDE:	Myeloma defining events
MGUS:	Monoclonal gammopathy of undetermined significance
MGRS:	Monoclonal gammopathy of renal significance
MIDD:	Monoclonal Ig deposition disease
MIP-1a:	Macrophage inflammatory protein1-alpha
MM:	Multiple Myeloma
MMSET:	Multiple myeloma set domain
M-protein:	Myeloma protein
MRI:	Magnetic resonance imaging
MYC:	Myelocytomatosis gene
NAT:	Nucleic acid test
NFK-β:	Nuclear factor kappa beta
NHLS:	National Health Laboratory Services
NNRTI:	Non-nucleoside reverse transcriptase inhibitor
NRAS:	Neuroblastoma-RAS (rat sarcoma virus)
NRTI:	Nucleoside reverse transcriptase inhibitor
NOS:	Not otherwise specified
OAF(s):	Osteoclast activation/activating factor/s
OI's:	Opportunistic infections

OPG:	Osteoprotegerin
OS:	Overall survival
PR:	Partial response
PD:	Progressive disease
PD-1:	Programmed cell death 1
PFS:	Progression free survival
PI:	Protease inhibitor
PIs:	Proteasome inhibitors
PLWH:	People living with HIV
POEMS:	Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin lesions
PR:	Partial response/remission
RANK:	Receptor activator of nuclear factor kappa-B
RANK-L:	Receptor activator of nuclear factor kappa-B ligand
RAS:	Rat sarcoma virus
R-ISS:	Revised international staging system
RR:	Relative risk
RRMM:	Relapsed, refractory multiple myeloma
SCT:	Stem cell transplantation
SD:	Standard Deviation
SD:	Stable disease
SLE:	Systemic lupus erythematosus
SREs:	Skeletal related events
SIV:	Simian immunodeficiency virus
3TC:	Lamivudine
TB:	Tuberculosis
TDF:	Tenofovir Disoproxil Fumarate
TGF-β:	Transforming growth factor beta
TNF-α:	Tumor necrosis factor alpha
TP53:	Tumour protein 53
UNAIDS:	The Joint United Nations Programme on HIV/AIDS
USA:	United States of America
VACS:	Veterans aging cohort study
VEGF:	Vascular endothelial growth factor
VGPR:	Very good partial response

VRd:	Velcade, Revlimid, Dexamethasone
VTE:	Venous Thromboembolism
WHO:	World Health Organization
Wnt:	Wingless-related integration site

1.0. CHAPTER 1: LITERATURE REVIEW

1.1. INTRODUCTION

Multiple Myeloma (MM) is a malignancy of plasma cells (1). The malignant plasma cells accumulate in the bone marrow and have the potential to infiltrate and damage vital organs. In addition, plasma cells secrete immunoglobulins which are detected in the urine and blood. An increase in immunoglobulins (hypergammaglobulinaemia) may be polyclonal, oligoclonal or monoclonal, and involve the immunoglobulins of different classes, primarily IgG, IgM and IgA. Polyclonal hypergammaglobulinaemia is usually caused by chronic infections and inflammation [including human immunodeficiency virus (HIV) and tuberculosis (TB)], chronic liver disease (such as cirrhosis), autoimmune disease [such as systemic lupus erythematosus (SLE)] and neoplastic disorders (carcinoma). The polyclonal increase in immunoglobulins is brought about by B-lymphocytes, which under the influence of cytokines, transform into antibody secreting plasma cells (1,2).

In MM, the increased proliferation of clonal plasma cells results in an increased production of one type of immunoglobulin, referred to as a monoclonal band or myeloma protein (M- protein). While MM is the prototype disorder resulting in a monoclonal gammopathy, monoclonal bands may be seen in the other plasma cell dyscrasias (including solitary plasmacytoma, Waldenstrom's macroglobulinaemia, Non-Hodgkin lymphoma, Chronic lymphocytic leukaemia, Primary amyloidosis and Heavy chain disease). Monoclonal gammopathies may also occur secondary to other disorders. These include rheumatological disorders such as rheumatoid arthritis, dermatological and neurological diseases, infections such as HIV, as well as neoplastic disorders, such as carcinoma of the breast, colon and prostate (1). Where the monoclonal band is not associated with any other disorder, it is designated as monoclonal gammopathy of undetermined significance (MGUS) (1).

1.2. EPIDEMIOLOGY

In 2020, world-wide, MM accounted for approximately 0.8-0.9% of all newly diagnosed cancers. The age standardized rate per 100 000 population was 2.2 and 1.5 for males and females, respectively (3).

The incidence of MM varies substantially across the different continents, with the highest rates reported in North America and some parts of Europe, intermediate rates in

other parts of Europe and Africa, and the lowest rates in Asia. Patients have been reported from all parts of the world, and no race or ethnic group is known to be immune. MM occurs more commonly in people of Afro-Caribbean descent, with the incidence being 2-fold higher in African Americans compared to Caucasians (1,4,5).

With regard to South Africa, in 2017, MM accounted for 0.51% and 0.44% of all newly (histologically) diagnosed cancers in males and females, respectively. The age standardized rate per 100 000 population was 1.05 and 0.7 for males and females, respectively (6). However, there appears to be under-reporting of MM cases in South Africa, as reporting is primarily based on histological evidence of the disease. Additionally, there is also a perceived lesser case-ascertainment of MM, as patients may be dying without the disease being suspected, or prior to the diagnosis being established (7). Despite this, MM is the second most common haematological malignancy in South Africa, after non-Hodgkin lymphoma (8). Further evidence in support of the perceived higher incidence of the disease in South Africa, is based on the study of Blattner et al, 1979, who surveyed MM cases in Johannesburg between 1973 and 1975 and found that the age-adjusted (world standard) rates for black males (4.47/100 000) and black females (5.1/100 000) closely resembled the incidence rates reported for blacks in the USA (9). MM is twice as common in Black Africans compared to Whites, and males are more commonly affected than females (1,5,7,9,10).

MM is characteristically a disease of the middle-aged and elderly. In the Western world, ninety-eight percent of cases occur over the age of 40 years with a peak in incidence in the seventh decade. The median age at diagnosis is 66 years (1,11). However, in Africa, the disease presents at a younger median age (approximately 5-10 years younger), with 7% of the patients being under the age of 40 years, based on a local study by Patel, 2000 (7). Furthermore, in his review of 170 patients with MM, studied between 1992 and 1997, the mean age at diagnosis was 61 years, and the male to female ratio was 1.45:1 (7). In 2016, van der Walt, in an extension to the above study at Chris Hani Baragwanath Academic Hospital (CHBAH), in his review of 289 patients with MM, seen between 1998 and 2010, showed a median age at diagnosis of 58 years, with a male to female ratio of 1:1. The peak age frequency (36.2% and 28.6%) in his study, was in the 6th and7th decades, respectively (12).

1.3. PATHOPHYSIOLOGY

The aetiology of the disease is largely unknown, but it is likely that environmental and genetic factors interact, resulting in an increased risk for MM. In addition to advancing age, male gender, African or African American ethnicity and MGUS, exposure to ionizing radiation, farming and agriculture, pesticides and petrochemicals have been shown to increase risk (7,13,14). The role of human herpes virus – 8 (HHV-8) is contentious (15), and the role of HIV, whether being causal or coincidental, is the subject of this research report, and will be discussed later, in further detail. There is also a potential role for MM risk and human leukocyte antigen (HLA) profiles, BRCA1 and BRCA2 mutations and single nucleotide polymorphisms (16). Locally, in a study done at CHBAH, a statistically significant positive association was shown with HLA-B18 and HLA-B35 and MM risk (17). Multi-step genetic and micro-environmental changes within the bone-marrow are required for the malignant transformation of post-germinal-center B cells (14,18).

MM is thought to evolve from MGUS to smoldering MM and finally to MM (18). In addition to genetic instability, failure of immune surveillance is another factor that is implicated in the progression to MM (18). MGUS arises from post-germinal-center plasma cells that regain their ability to proliferate. The pathogenic mechanisms thought to be responsible for this transition include extra chromosomes contributing to a hyper-diploid state and chromosome translocations which result in the placement of oncogenes next to immunoglobulin transcriptional regulatory genes (18,19).

Primary early chromosomal translocations occur at the immunoglobulin switch region on chromosome 14 (q32.33), which is commonly juxtaposed to musculoaponeurotic fibrosarcoma (MAF) gene - (t[14;16][q32.33;23]), and multiple myeloma set domain (MMSET) in all cases and fibroblast growth factor receptor (FGFR3) in 30% of cases (19). A second hit is required for transition from MGUS to MM and includes secondary gene translocations, epi-genetic changes and bone-marrow stromal changes (18).

Secondary late-onset translocations and gene mutations that are implicated in the progression of disease include complex karyotypic abnormalities in MYC (myelocytomatosis gene), the activation of neuroblastoma-RAS (rat sarcoma virus) – NRAS and Kirsten rat sarcoma virus -RAS (KRAS), mutations in FGFR3and tumour protein 53 (TP53), as well as the inactivation of cyclin-dependent kinase inhibitor 2A (CDKN2A) and cyclin-dependent kinase inhibitor 2C (CDKN2C) (13,14,18).

Smoldering MM progresses to MM at a rate of approximately 10% per year over the

first 5 years after diagnosis, 3% per year over the next 5 years, and 1.5% per year, thereafter. The rate of progression is determined by the underlying cytogenetic changes, with t(4;14), del(17p) and gain(1q) carrying a higher risk of progression (20,21).

1.4. CLINICAL PRESENTATION

1.4.1. Bone disease

Bone disease or skeletal related events (SREs) constitute the most important and most common clinical problem in MM. Based on our local data (percentages are indicated in brackets), together with infection (27-60%) and renal impairment (16-32%), SREs constitute 1 of the 3 dominant clinical manifestations of the disease (7,12). Most of the patients in the local setting are symptomatic, with bone pain (87-94%) and anaemia (81-92%) comprising the most common symptom and sign of the disease, respectively (7,12). Skeletal related events include (7):

i) Bone pain (94%)
ii) Osteolytic bone lesions on radiological imaging (89%)
iii) Pathological fractures of the long bones and ribs (15%)
iv) Vertebral body compression fractures (50%)
v) Osteopenia/osteoporosis
vi) Hypercalcaemia (40%)
vii) Spinal cord compression, and
viii) Infiltration of the bone marrow resulting in cytopenias such as anaemia (1,7,12,22).

Bone pain is typically the presenting symptom in MM, and is associated with significant morbidity, limiting the quality of life of the patient. Common sites of bone pain include the back (especially the mid and lower back), thorax (ribs and sternum), as well as the long bones. Osteolytic bone lesions are characteristic, as MM is an osteoclastic rather than osteoblastic disease. Osteolytic bone lesions may be complicated by pathological fractures, with exacerbation of bone pain. Vertebral-body compression fractures may result in pain, loss of height and may also contribute to paralysis of the lower extremities. Significant osteopenia, with or without osteoporosis is also a feature of the disease (1,7,10,12,22,23).

MM bone disease results from increased activity of osteoclasts (as a result of elaboration of osteoclast-activating factors – OAF's, from the MM cells and the bone marrow microenvironment) and decreased activity of osteoblasts, resulting in osteolytic bone lesions (10,22). OAF'S include IL-1 (Interleukin-1), lymphotoxin, VEGF (vascular

endothelial growth factor), RANKL (receptor activator of nuclear factor kappa-β ligand), MIP-1α (macrophage inhibitory protein 1α), and TNF (tumour necrosis factor).

As indicated above, increased osteoclast activity is due to stimulation by (RANKL) which is produced when plasma cells adhere to bone marrow stromal cells and osteoblasts (10,22,23). The binding of RANKL to RANK (receptor activator of nuclear factor kappa-β) promotes osteoclast maturation and activation (10,22,23). Osteoprotegerin (OPG) is a glycoprotein that is secreted by bone marrow stromal cells. It acts as a decoy receptor for RANKL and blocks the RANKL-RANK interaction resulting in inhibited osteoclast differentiation and function, with resultant suppression of osteoclastogenesis (24).

Interleukin-6 (IL-6) is produced by plasma cells and bone marrow stromal cells and is a growth factor for osteoclasts and myeloma cells resulting in proliferation as well as preventing their apoptosis. Interleukin-1beta (IL-1b) enhances the expression of adhesion molecules and induces paracrine IL-6 production (23). Macrophage inflammatory protein 1-alpha (MIP-1a) is a member of the CC (chemokine) family and is concerned with cell adhesion and migration. It is produced by myeloma cells and has been shown to directly stimulate osteoclast formation and differentiation (25).

Interleukin-3 (IL-3) in combination with MIP-1a or RANKL significantly increases the formation of osteoclasts and bone resorption compared to MIP-1a or RANKL alone. IL-3 mRNA levels were found to be elevated in myeloma cells and IL-3 protein levels were increased in bone marrow aspirates from MM patients (26). Tian, et al, 2003, reported that myeloma cells produce a protein called dickkopf1 (DKK1) that inhibits the wingless-related integration site (Wnt) signaling pathway that is essential for osteoblast differentiation with resultant decreased osteoblastic activity (27).

1.4.2. Renal dysfunction

Renal dysfunction is a common complication in MM, resulting in significant morbidity. The cause of renal dysfunction is multifactorial and includes the toxic effects of monoclonal light chains on renal structures. Monoclonal light chains cause renal damage by distinct mechanisms on various segments of the nephron, including a tubulopathy and obstructive uropathy. Myeloma cast nephropathy (also known as ‘myeloma kidney’ or plasma cell infiltration of the kidney with casts) is an important cause of renal failure. Accumulation and precipitation of light chains in the distal tubules with Tamm-Horsfall protein (uromodulin) results in renal obstruction (22,28).

Furthermore, monoclonal light chains are directly toxic to the proximal renal tubules. Both lambda and kappa light chains have been found to be nephrotoxic, but lambda light chains are more frequently involved in the formation of amyloidogenic proteins, with a resultant glomerulopathy (28). Additional damage in the 'myeloma kidney' results from endocytosis of light chains by renal tubular cells with resultant production of pro-inflammatory cytokines such as IL-6, interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) via activation of nuclear factor kappa-ß (NFK-ß) and mitogen-activated protein kinases (MAPK) (28-30).

Hypercalcaemia is another common cause of renal impairment in MM (7,10,22,31). Hypercalcaemia results from increased osteoclast activation due to the elaboration of OAF's. Various mechanisms are thought to cause renal injury. Hypercalcaemia causes spasm of the renal afferent arteries with a reduction in glomerular filtration rate. Interstitial nephritis and polyuria with subsequent dehydration due to an inability of the kidneys to concentrate the urine (nephrogenic diabetes insipidus), with resultant decreased reactivity to antidiuretic hormone (ADH) also contributes to renal impairment (31). Chronic calcium deposition in the kidneys (nephrocalcinosis) results in tubulo-interstitial injury and fibrosis. Hypercalcaemia resulting in nephrocalcinosis and renal stones is a less likely problem in MM, due to the subacute or acute nature of presentation in MM patients, compared to other causes of hypercalcaemia, such as hyperparathyroidism.

Light- chain glomerulopathy is caused by the deposition of immunoglobulins in the form of amyloid and non-amyloid protein. Non-selective proteinuria is the dominant syndrome in both forms of light chain glomerulopathy (28). In immunoglobulin (Ig) light-chain amyloidosis (AL), the immunoglobulin deposits consist of N-terminal fragments of the variable regions of light chains. Non-amyloid monoclonal Ig deposition disease (MIDD) is characterized by nodular sclerosing glomerulopathy, proteinuria and renal dysfunction. Histological changes include monoclonal light and/or heavy chain deposits within the basement membranes of glomeruli, tubules and blood vessels. Three subtypes of MIDD have been described, including light chain deposition disease (LCDD), light and heavy chain deposition disease (LHCDD) and heavy chain deposition disease (HCDD). LCDD is the most prevalent (32). Rarely, tubular dysfunction can result from an acquired Fanconi syndrome, manifesting with glycosuria, aminoaciduria and phosphaturia (33).

Other contributors to renal dysfunction include: hyperuricaemia (including interstitial nephritis and renal stones), urinary tract infections, nephrotoxic drugs (such as the non-steroidal anti-inflammatory agents, aminoglycosides, bisphosphonates and contrast media), amyloid related proteinuria, glomerulonephritis and nephrotic syndrome, hyperviscosity, which interferes with the normal counter-current mechanism in the kidney, and co-morbidities such as hypertension and diabetes (1,7).

1.4.3. Anaemia

Anaemia is the most common presenting physical sign in MM (1,7,10). More than two-thirds to three-quarters of the patients with MM, have anaemia at presentation and it is even more common among patients with recurrent or progressive disease. Anaemia is a significant contributor to the fatigue and impaired quality of life in MM patients. There are multifactorial causes for anaemia in MM. These include: i) Infiltration of the bone marrow by disease, ii) Anaemia of chronic disease, iii) Renal dysfunction, iv) Bleeding (secondary to platelet dysfunction, drugs such as the non-steroidal anti-inflammatory agents, thrombocytopenia, coagulation factor dysfunction - related to the paraprotein, hyperviscosity, AL amyloidosis with acquired factor deficiencies and acquired von Willebrand's disease), v) Nutritional factors (including vitamin B12 deficiency) and vi) Therapy (including chemotherapy and radiotherapy). The anaemia is usually normochromic/normocytic, but may be microcytic with blood loss, or macrocytic with concomitant vitamin B12 deficiency (7,10,34).

Patients with MM associated renal disease have decreased levels of erythropoietin (EPO) and patients without renal dysfunction have been shown to have a blunted response to EPO (35). Interleukin-1 (IL-1), TNF, transforming growth factor ß (TGF-β) and interferon-gamma (IFN-γ) are produced by the tumor as well as the normal host cells. These cytokines are involved in the sequestration of iron in the reticulo-endothelial system, gastrointestinal tract and the hepatocytes. Furthermore, they may also interfere with EPO production in the kidneys and have direct inhibitory effects on erythroid precursors and erythropoiesis (36).

Hepcidin is a peptide produced in the liver and is implicated in the anaemia of chronic disease/inflammation (increased hepcidin expression). Sharma, et al, 2008, showed that hepcidin is upregulated in MM by IL-6 dependent and independent mechanisms (37). It has also been reported that anaemia may be due to decreased red blood cell precursors as a result of increased FAS-Ligand expression on malignant plasma cells which induce

apoptosis (38). Other cytopenias, including leucopenia and thrombocytopenia are uncommon at presentation, and occur in less than 10% of patients with MM, at presentation, but become more prevalent with therapy and progression of the disease (7).

1.4.4. Infection

Infectious complications are a major cause of morbidity and mortality in MM patients. Up to 10% or more of the patients die at the initial presentation, and a significant proportion of the early deaths are the result of infection (39). The increased susceptibility to infection is multifactorial, but impaired immunoglobulin (antibody) production or increased catabolism, resulting in decreased normal immunoglobulin levels or immunoparesis, appears to be the major cause. Other causes include leucocyte dysfunction (defective opsonization, decreased granulocyte adhesiveness and impaired leukocyte migration), impaired T cell function (cell-mediated immune dysfunction), neutropenia secondary to myelosuppressive and immunosuppressive therapy, use of corticosteroids and impaired defenses against infection, secondary to pain, increasing age and immobility (1,10,40).

1.4.5. Neurological complications

Neurological complications of MM may be directly attributed to the disease or occur indirectly from complications of the disease or therapy. Each of these disease mechanisms may affect the central or peripheral nervous system. Direct involvement may be due to a plasmacytoma or due to the abnormal paraprotein (heavy or light chain component), whereas indirect involvement may result from the following: i) Infections (examples include pneumonia with hypoxaemia, meningitis etc.), ii) Metabolic and electrolyte imbalance (including hypercalcaemia, uraemia, hyponatraemia, hypoglycaemia etc.), iii) Bleeding (secondary to thrombocytopenia, DIC, platelet and coagulation factor dysfunction, including acquired factor deficiencies etc.), iv) Hyperviscosity (ocular changes, thrombosis, bleeding) v) Vitamin B12 deficiency, vi) AL-amyloidosis (manifesting with peripheral neuropathy) and vii) Therapy. Examples of neurological manifestations related to therapy include: a) Corticosteroids – emotional lability, confusion, depression, proximal myopathy, thrombosis., b) Immunomodulatory agents such as thalidomide – peripheral neuropathy, sedation, thrombosis., c) Proteosome inhibitors such as bortezomib – peripheral neuropathy)., d) Chemotherapy such as vincristine – peripheral neuropathy, myelosuppression with intracranial bleeding and infectious complications)., d) Radiation - myelitis etc. (1,7,10,39).

As indicated above, direct involvement of the nervous system may manifest with the effects of the disease, particularly in the form of plasmacytomas, which occur in any location in the central or peripheral nervous system, as well as other bony sites such as the cranium, sternum, clavicles, vertebrae, ribs, pelvis, long bones etc. and potentially in any other part of the body. Plasmacytomas may cause neurological deficits, most importantly spinal cord compression (SCC), due to their extradural localization. Other contributors to SCC include vertebral compression fractures and ischaemia to the spinal cord (1,7,10).

As indicated above, neuropathies are also a feature of MM, whether it is a peripheral neuropathy, mononeuropathy or cranial neuropathy. In neuropathies without evidence of disease affection, therapy, or amyloid infiltration, the aetiology is likely multifactorial and may include nutritional deficiency (e.g., vitamin B12 deficiency) or metabolic factors (such as renal impairment), or other co-morbidities, such as diabetes mellitus (39,41,42).

A much less common variant of MM, solitary plasmacytoma of bone, may be associated with one or all of the following features: polyneuropathy, organomegaly, endocrinopathy, monoclonal ('M') protein and skin changes known as the POEMS syndrome. Although accounting for only 5% of cases of myeloma, 85% of patients with POEMS syndrome have a neuropathy (43).

1.4.6. Other complications

Other complications, in addition to the bone disease or skeletal related events, infection, renal impairment, neurological disease, cytopenias (mentioned under anaemia), hyperviscosity and bleeding (the causes of which have been included under anaemia, above), include i. plasmacytomas (whether osseous and/or extra-osseous, solitary, extramedullary, or multiple) and their consequences – mass lesions, compression, pain, fractures etc., ii. AL amyloidosis manifesting with renal, hepatic, haemostatic, dermatological and neurological abnormalities, in addition to classically presenting with macroglossia, shoulder pad infiltration and cardiac involvement (restrictive cardiomyopathy, diastolic dysfunction and conduction disturbances) and iii. thrombosis. MM patients are at an increased risk of both arterial and venous thrombosis, with VTE (venous thromboembolism) occurring in up to 5-10% of patients. Risk factors for VTE include immobility, use of central venous catheters, pre-existing or acquired abnormalities in coagulation factor or platelet function and therapy [such as the use of

corticosteroids (e.g. dexamethasone), immunomodulatory agents (thalidomide, lenalidomide, pomalidomide) and erythropoietin]. Arterial thrombosis is typically related to arterial risk factors, including hypertension, diabetes, hypercholesterolaemia, smoking and advanced age (1,7,10,39,44).

1.5. DIAGNOSIS

The revised International Myeloma Working Group (IMWG) criteria for the diagnosis of MM requires the following:

i) Symptomatic patient (bone pain, fatigue, infections, fractures, renal impairment etc.)

ii) Presence of clonal bone-marrow (BM) plasma cells in excess of 10% in the bone marrow or biopsy proven bony or extramedullary plasmacytoma.

iii) Presence of a paraprotein in the serum or urine, and

iv) Evidence of underlying end organ damage (CRAB – Calcaemia, Renal insufficiency, Anaemia, Bone lesions) OR the presence of ≥ 1 'biomarker' of malignancy, which is also referred to as a myeloma defining event (MDE). The 'biomarkers' include: a. clonal BM plasma cells ≥ 60%, b. involved: uninvolved serum free light chain (FLC) ratio ≥ 100, with involved FLC ≥ 100 mg/L, and c. >1 focal lesion found on magnetic resonance imaging (MRI), which measures greater than 5mm (45) (see Appendix C). Each of the biomarkers is associated with an 80% risk of progression to symptomatic end-organ damage (45).

1.6. STAGING

Staging systems in MM, among others include the Durie-Salmon staging system and the International Staging System (ISS). The former correlates the myeloma cell mass to the damage done to certain vital organs (bone marrow, bones, kidney). The haemoglobin (Hb), serum calcium, M-protein, severity of osteolytic bone lesions and serum creatinine are used to determine the stage and predict prognosis (see Appendix D) (46).

The ISS uses the albumin level and beta-2-microglobulin (B2M) level in various combinations, to predict prognosis (see Appendix E) (47). The Revised ISS (R-ISS) includes, in addition to the ISS, the presence of high-risk cytogenetic abnormalities such as the presence of del(17p), t(4;14), t(14;16) and t(14;20) and an elevated lactate dehydrogenase (LDH) level (48).

1.7. TREATMENT

1.7.1. Supportive care

Supportive therapy in MM includes:

a) Educational and psychosocial support, with regard to the disease, treatment, follow up and complications
b) Treatment of cytopenias: correction of reversible factors including the use of haematinics (e.g.vitamin B12), growth factors such as EPO and blood and blood products where necessary
c) Diagnosis and management of infections: infection prophylaxis and vaccinations where indicated, appropriate use of antibiotics and GCSF (granulocyte colony stimulating factor), IVIg (intravenous immunoglobulin) replacement where necessary
d) Correction of fluid and electrolyte imbalance: optimal fluid intake, rehydration, use of allopurinol, bisphosphonates for hypercalcaemia and denosumab for bone disease
e) Physiotherapy, occupational therapy, back support - use of a corset/brace/walker etc., modification of the living/home environment, kyphoplasty and vertebroplasty where indicated
f) Other: Plasmapheresis/exchange for hyperviscosity, dialysis for renal failure, anticoagulation, where indicated, for thrombosis prophylaxis or treatment, treatment of other co-morbidities, etc. (1,10,22).

1.7.2. Specific treatment

Specific therapy includes the following modalities of treatment:

i. Combination therapy / 'chemotherapy' using one or more of the following groups of drugs in combination: a. cytotoxics, b. corticosteroids, c. immunomodulatory agents (IMiDs), d. proteasome inhibitors (PIs) and e. monoclonal antibodies

ii. Radiotherapy – for spinal cord compression, plasmacytomas, severe unremitting pain

iii. Surgery – ORIF (open reduction and internal fixation) for pathological fractures, decompression and laminectomy for spinal cord compression, where indicated

iv. Stem cell transplantation (SCT), with particular reference to autologous SCT

v. Newer and experimental agents – including next generation novel agents and cellular therapies, such as CAR-T cells (chimeric antigen receptor T-cells) (1,10,22)

1.7.2.1. Newly diagnosed Multiple Myeloma

Newly diagnosed patients may be transplant eligible or ineligible. Younger patients

(generally ≤ 65-70 years), who are transplant eligible, are offered induction therapy, followed by consolidation therapy in the form of an autologous stem cell transplant (ASCT) ± short term consolidation chemotherapy, and maintenance therapy. Patients that are not eligible for an ASCT due to age or co-morbid disease (which includes, in our local setting, patients with established, irreversible, end-stage renal failure, ongoing paraplegia despite the use of corticosteroids, chemotherapy and radiotherapy, as well as any severe, irreversible, vital organ dysfunction/failure) are offered induction chemotherapy followed by maintenance therapy (1,10,45,49,50).

Induction therapy is made up of various combinations of drug classes, including: i) Corticosteroids (such as dexamethasone), ii) IMiDs such as thalidomide, lenalidomide or pomalidomide, iii) PIs such as bortezomib, carfilzomib or ixazomib and more recently, iv) Monoclonal antibodies (such as daratumumab), while maintenance therapy includes drugs such as thalidomide, lenalidomide, bortezomib or ixazomib, usually as a single agent or in combination with a corticosteroid. In order to guide treatment, patients are classified into standard and high-risk groups based on cytogenetic studies. Standard risk patients include trisomies and translocations t(11;14) and t(6;14). High risk patients include those with translocations t(4;14), t(14;16), t(14;20) and del(17p) and gain(1q) (10,49,50).

As an example, standard risk patients eligible for an ASCT receive 4-6 cycles of Velcade (bortezomib), Revlimid (lenalidomide) and dexamethasone (VRd) followed by either an early ASCT or cryopreservation of stem cells and an additional 4-8 cycles of VRd. In the second option, ASCT is deferred until relapse. Both options are followed by lenalidomide maintenance. High risk patients eligible for transplant receive 4-6 cycles of VRd or daratumumab with VRd followed by early ASCT and bortezomib maintenance. Standard risk patients who are not eligible for ASCT receive 8-12 cycles of VRd with lenalidomide maintenance. High risk patents not eligible for ASCT receive 8-12 cycles of VRd, followed by bortezomib maintenance (49-52).

Other treatment options for non-eligible ASCT patients includes an initial combination of melphalan, prednisone/dexamethasone and an immunomodulatory drug such as thalidomide or lenalidomide. Treatment is continued until a stable ‘plateau phase’ is reached, after which a single drug can be used as maintenance therapy (49-52).

A tandem or double ASCT may be indicated if there is failure to achieve a CR (complete response), defined as a negative immunofixation (serum and urine) and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in the bone

marrow, or at least a VGPR (very good partial response), defined as a serum and urine M protein detectable by immunofixation, but not on electrophoresis, or ≥ 90% reduction in the serum M protein and urine M protein < 100 mg/24 hours (22,53).

1.7.2.2. Relapsed, Refractory Multiple Myeloma (RRMM)

Almost all patients with MM have relapse of disease and the remission periods between disease relapses decrease with each subsequent treatment regimen. The median progression-free survival (PFS) and overall survival (OS) in patients with relapse disease, refractory to lenalidomide and bortezomib was low prior to the introduction of daratumumab (52).

Treatment options for RRMM include: i. Novel agents – IMiDs and PIs, ii. Combination therapies, such as novel agents with cytotoxics or monoclonal antibodies, iii. Salvage ASCT, and iv. Experimental therapy/clinical trials. In general, the choice of therapy depends on a. Disease related factors – cytogenetics, ISS stage, b. Treatment related factors – prior therapy and response to prior therapy (efficacy), toxicity, availability of second and third generation novel agents and newer therapies, and c. Patient related factors – age, performance status, major organ function, co-morbidities, etc. (54).

As an example, in first-time relapse patients who are not refractory to lenalidomide, daratumumab, lenalidomide and dexamethasone (DRd) is the preferred treatment choice. Kyprolis (carfilzomib), lenalidomide and dexamethasone (KRd); elotuzumab, lenalidomide and dexamethasone (ERd); and ixazomib, lenalidomide and dexamethasone (IRd) are acceptable alternatives (45,50,54). In patients who are refractory to lenalidomide, daratumumab, bortezomib and dexamethasone (DVd) is recommended. Alternative regimens include daratumumab, pomalidomide and dexamethasone (DPd); isatuximab, pomalidomide and dexamethasone (Isa-Pd) and elotuzumab, pomalidomide and dexamethasone (EPd) (45,54).

Salvage ASCT should be considered in patients who are eligible and have not had a transplant before.

For patients who have had a prior ASCT, a 2nd ASCT should be considered if they had a > 36-month response with maintenance therapy following the 1st ASCT (45,54).

The role of allogeneic stem cell transplantation and CAR-T cell therapy in MM is beyond the scope of the discussion, with regard to this research report.

1.8. OUTCOME

MM has a variable course with a median PFS period of 66, 42 and 29 months for R-ISS stage I, II and III disease, respectively and a 5-year OS rate of 82%, 62% and 40%, respectively (48).

Data from randomized controlled trials using modern therapy with novel agents, demonstrate a 6-year median survival, and a median OS of approximately 80% (48, 49,51,53,55). In the subset of patients eligible for ASCT, a 4-year survival rate above 80% has been demonstrated. However, the median OS is lower in the elderly (age >70 years) (51).

A more accurate estimation of prognosis depends on multiple factors that include primary cytogenetic abnormalities such as trisomies and translocations of the plasma cell clone and secondary cytogenetic abnormalities. Additional markers associated with aggressive disease biology are an elevated LDH level and evidence of circulating plasma cells on the peripheral smear. Median OS in standard risk patients is 6-8 years, while in high-risk patients is approximately 3-5 years, with the potential for improved survival with appropriate and optimal treatment, using novel and evolving therapies (55).

1.9. HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

1.9.1. History of HIV

Acquired immunodeficiency syndrome (AIDS) was first recognized in 1981, with the subsequent recognition of a retrovirus, now known as human immunodeficiency virus (HIV), being identified as the causative agent. Two lentiviruses, HIV-1 and HIV-2 cause disease in humans. Both HIV viruses are the result of multiple cross-species transmissions of simian immunodeficiency viruses (SIVs) that are found in African primates (56). HIV-1 is more prevalent than HIV-2 as a result of it being more pathogenic (57).

1.9.2. Epidemiology

In 2020, globally there were 36 million adults with HIV-1 of which 67% were living in sub- Saharan Africa. Women accounted for 63% of all new HIV-1 infections, compared to men with 37% (58).

The Joint United Nations Program on HIV/AIDS (UNAIDS) reports regularly on the estimated burden of HIV-1 infection in each country. The countries with the highest burden, per capita, include Swaziland, Lesotho, Botswana and South Africa. South Africa has the highest number of HIV-1 seropositive patients in the world (59). Furthermore, the HIV seroprevalence in Gauteng, among adults aged 25 years and older, was 14.9% (2005), 14.4% (2008), 18.8% (2012) and 18.7% (2017) according to the South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, which is conducted every three to five years. The most recent survey was published in 2017 (60). Lastly, HIV-1 infection is one of the main causes of morbidity and mortality globally (61).

1.9.3. Pathophysiology

HIV-1 is a retrovirus and is thus able to integrate its DNA into the host genome making it difficult to eradicate with currently available therapies. After the single-strand RNA is reverse transcribed into HIV-1 DNA and integrated into the host genome, host enzymes transcribe HIV-1 DNA and produce mRNA resulting in the production of mature virions (57).

The primary receptor for HIV-1 is cluster of differentiation-4 ($CD4^+$), expressed on the surface of T lymphocytes, monocytes, macrophages and dendritic cells. However, a co-receptor is required to enter the host cell. Either one of the chemokine receptors (CCR), chemokine receptor type 5 (CCR5) or C-X-C chemokine receptor type 4 (CXCR4) are used depending on the HIV-1 variant. CCR5 and CXCR4 are differentially expressed on some T lymphocyte subsets. CCR5 is expressed at high levels in memory T lymphocytes but not on naïve T lymphocytes and CXCR4 is expressed on both. Furthermore, CCR5 is expressed on macrophages and dendritic cells. The preferred target cells for infection are activated T lymphocytes, whereas for unknown reasons, resting cells are less prone to infection. Dendritic cells are difficult to infect but are capable of sequestering the virus and infecting neighboring cells (57).

After a transmission event, HIV-1 targets $CD4^+$ T lymphocytes in mucosal tissues and

within days spreads to the lymphoid organs (62). HIV-1 is capable of establishing latent infection within memory $CD4^+$ T lymphocytes which are maintained indefinitely through homeostatic proliferation (63). The lymph nodes that harbor the virus act as a sanctuary site due to limited antiretroviral drug penetration and limited host clearance mechanisms (64,65).

One hallmark of the HIV-1 virus is the high rate of genetic variation that is estimated at one mutation for every few replication events. The high error rate coupled with a high viral replication rate results in extensive variation in HIV-1 (selection forces). Envelope sequences from different individuals who have been infected by different HIV-1 subtypes differ on average by 25% and by as much as 35% (66).

The HIV-1 virus causes depletion of circulating and tissue-based $CD4^+$ T lymphocytes. A vast majority of HIV-1 replication, and $CD4^+$ T lymphocyte death, occurs in gut-associated lymphoid tissue resulting in increased permeability of the intestinal lining. Systemic translocation of bacterial products leads to chronic immune activation (67). Several mechanisms contribute to the depletion of $CD4^+$ T lymphocytes. The replication of the virus is directly cytopathogenic but does not account for all cell death (68).

HIV-1 infection of lymphocytes can lead to the generation of incomplete HIV-1 DNA reverse transcripts resulting in an intense inflammatory response with destruction of local uninfected cells (68). A sustained increase in the frequency of proliferation and activation of $CD4^+$ T lymphocytes and cluster of differentiation-8 ($CD8^+$) T lymphocytes contribute to the progressive loss of these cells. The degree to which HIV-1 infection causes T lymphocyte activation is an independent predictor of the rate of $CD4^+$ T lymphocyte loss and progression to AIDS (69). Lastly, HIV-1 infection negatively affects the immune system's capacity to regenerate new $CD4^+$ T lymphocytes by causing harm to stem cells and the thymus (70).

1.9.4. Primary infection

Most patients are asymptomatic but the detection of viral RNA in the blood is often associated with a short symptomatic phase characterized by fever, non-specific rash, generalized lymphadenopathy and myalgia. More severe complications include meningitis. The severity of symptoms correlates strongly with the peak in HIV-1 viral load (approximately 10^6-10^7 copies per ml) (71). After the immune response develops, the viral load decreases by 100-fold to a steady-state level or viral load set point (72).

A 100-fold decrease in viral load as acute infection resolves is mainly attributed to the development of HIV-1 specific $CD8^+$ cytotoxic T lymphocytes (CTLs). Eventually, the immune response fails to control the virus due to upregulation of the inhibitory receptor, programmed death 1 (PD-1), on $CD8^+$ T lymphocytes which leads to impaired function and failure of viral suppression (73). During the initial stage of primary infection, a transient drop in $CD4^+$ T lymphocyte counts is typically noted. After the primary infection resolves, $CD4^+$ T lymphocyte counts recover to near-normal levels that persist for many years followed by eventual decline (67). Clinical outcome has been shown to correlate with a high viral load set point. Patients with high viral load set points typically progress more rapidly to AIDS and death compared to low viral load set points. Very few individuals have very low viral load set points and are termed HIV elite controllers (74). Most of the knowledge regarding immune mechanisms for HIV-1 control in vivo is derived from the study of elite controllers. Human Leukocyte antigen-B*5701 (HLA-B*5701) and other HLA alleles are associated with control of HIV-1 infection in the absence of therapy (75,76).

1.9.5. Risk factors for HIV acquisition

HIV-1 is transmitted through contact of infected body fluids with mucosal tissue or broken skin and transfusion of infected blood products. Increased infectiousness has been shown to be directly proportional to HIV-1 viral load in plasma and genital secretions (77). Viral characteristics that are related to increased infectivity include higher envelope content, increased cell-free infectivity, improved dendritic cell interaction and relative resistance to Interferon alpha (IFN-a) (78).

HIV-1 seronegative patients are more susceptible to infection, if they have increased numbers of potential target cells (activated $CD4^+$ T lymphocytes) at the site of exposure. Such sites include areas of trauma, areas infected with another sexually transmitted disease and the foreskin (62,79).

Long-acting injectable hormonal contraception has also been linked to increased HIV-1 infection rates in observational studies. Possible causes include thinning of the vaginal epithelium, increased number of activated $CD4^+$ T lymphocytes and reduced condom use (80).

Use of drugs, intravenous and non-intravenous, increases the risk of HIV-1 infection. Social and structural factors also contribute to increased risk for HIV-1 infection.

Smaller sexual networks may enable more rapid dissemination of HIV-1 than larger networks. HIV-1 is also more likely to spread through sexual networks with a large percentage of undiagnosed and untreated sexual partners (57).

1.9.6. Diagnosis

In the United States, the Centre's for Disease Control (CDC) and Prevention recommend that screening be performed with a 4th generation antigen/antibody immunoassay which detects antibodies to HIV-1 and HIV-2, as well as the p24 antigen. The p24 antigen is a viral protein produced by HIV-1 and HIV-2 and allows for earlier detection of infection. If non-reactive results are obtained, then no further testing is required. If a reactive test result is obtained, a supplemental antigen/antibody immunoassay that can differentiate between HIV-1 and HIV-2 should be performed. If the supplemental test is non-reactive or indeterminate, aHIV-1 nucleic acid test (NAT) should be performed (81).

The South African National HIV testing services policy of 2016 consists of screening with a rapid antigen test, and if positive, a confirmatory rapid antigen test of a different make is performed. If the repeat test is positive, then the patient is diagnosed as having HIV-1 infection. If the repeat HIV test is negative, a repeat of the test algorithm is recommended. If discrepant results are obtained, an enzyme-linked immunosorbent assay (ELISA) is performed (82).

1.9.7. Treatment

The World Health Organization (WHO) 2019 Updated Recommendations on the use of highly active antiretroviral therapy (HAART) in HIV-1 seropositive adults advocates the use of a 3-drug regimen that includes 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 Non-nucleoside reverse transcriptase inhibitor (NNRTI). The recommended first-line regimen includes tenofovir disoproxil fumarate (TDF) with either lamivudine (3TC) or emtricitabine (FTC) and dolutegravir (DTG) (83).

The South African National Consolidated Guidelines of 2020 recommend a 3-drug regimen of TDF, 3TC and DTG as the initial treatment (84).

1.9.8. Complications of HIV and Treatment

Treatment does not fully restore immune function and consequently, several

inflammation-associated and immunodeficiency complications occur. Cumulative toxicities from chronic exposure to HAART causes metabolic disturbances and potentially end-organ damage. Studies conducted in high income countries have shown that HIV-1 infected adults, shown to have treatment- mediated HIV-1 viral suppression, are at risk for developing several non-AIDS conditions that include cardiovascular disease, kidney disease, liver disease, osteopenia/osteoporosis and neurocognitive disease (85).

HIV-1 infected adults are also, like the general population, at risk for hypertension and diabetes, both of which are increasingly recognized as major health problems in Africa. Increased smoking in South Africa may influence the epidemiology of co-morbidities seen in patients with chronic HIV-1 infection and include lung, renal and liver disease. Metabolic changes like body fat redistribution, insulin resistance, diabetes mellitus and hyperlipidaemia are associated with a cumulative exposure to HAART. Consequently, treatment guidelines advocate regimens based on their long-term toxicity (85).

Increased levels of IL-6 in HIV-1 infected patients, have been shown in large international multi-site studies to positively correlate with all-cause mortality. Other well-validated biomarkers include soluble CD14 and soluble CD163 which have been shown to be associated with an increased risk of death, and increased risk of coronary artery inflammation and atherosclerosis, respectively (85).

HIV-1 infected patients are at an increased risk for kidney disease. There are multiple causes, which include HIV-associated nephropathy (HIVAN), non-collapsing focal segmental glomerulosclerosis (FSGS), immune-complex kidney disease, comorbid kidney disease, chronic exposure to HAART and opportunistic infections. Glomerular-dominant diseases can be divided into those that result from podocytopathies and those that result from immune-complexes. Subtypes of podocytopathies in HIV-1 infection include classic HIVAN, FSGS not otherwise specified (NOS), and rarer cases of minimal change disease and diffuse mesangial hypercellularity. All exhibit extensive podocyte foot process effacement and proteinuria. Tubulointerstitial disease occurs invariably in HIVAN, causing kidney enlargement and a hyperechoic appearance on sonography (86).

In patients treated with HAART, non-collapsing FSGS(NOS) is more commonly encountered on renal biopsy and the findings may be difficult to distinguish from arterio-nephrosclerosis of hypertension, aging and apolipoprotein L1 (APOL1) associated nephropathy. Causality is presumed once other causes for FSGS have been excluded.

Numerous forms of immune-complex mediated glomerular disease occur in HIV-1 infected patients. The disease spectrum is heterogenous and HIV-1 causality in most cases is unclear. In addition to lupus nephritis, a lupus-like nephritis with positive immune staining but negative serologies and absent clinical signs of systemic lupus erythematosus (SLE) has been reported in HIV-1 infected patients (86).

IgA nephropathy may be due to under-galactosylated IgA1 or due to deposition of IgA directed to viral antigen. “Ball-in-cup” lesions due to subepithelial deposits have been reported in cases from South Africa (86).

Tubulointerstitial disease may occur due to acute tubular necrosis (ATN), as a consequence of sepsis, volume depletion and toxic insults. TDF may cause a proximal tubulopathy with dysmorphic appearing mitochondria. Tubulointerstitial nephritis can result from protease inhibitors (PI) and mycobacterial infection. Diffuse infiltrative lymphocytosis syndrome (DILS) is a hyperimmune reaction to HIV-1 that involves the kidneys in approximately 10% of cases. Immune reconstitution inflammatory syndrome (IRIS), after HAART initiation rarely involves the kidneys. Both conditions demonstrate $CD8^+$ T lymphocyte infiltrates. Any drug, antiretroviral or other, may cause interstitial nephritis. The PIs, atazanavir and indinavir are the most common causes noted (86).

Despite increased efforts to diagnose HIV-1 infection before the development of advanced disease, opportunistic infections (OIs) continue to occur in the era of HAART. Most OIs occur in patients with $CD4^+$ T lymphocyte counts below 200 cells/ul but, even in those with higher counts, a small residual risk remains. Oesophageal candidiasis, Kaposi’s sarcoma and pulmonary mycobacterium tuberculosis (TB) are the most common infections experienced in the latter group. Mycobacterial tuberculosis and cryptococcal infections account for a significant proportion of the OIs seen (87).

The lung is one of the most frequently affected sites in HIV/AIDS. Complications occur predominantly due to opportunistic infections. Lower respiratory tract infections occur at a 25-fold increased rate, compared to the HIV-1 seronegative population. Currently, in developed countries, bacterial pneumonia is the most common cause of pulmonary infections in HIV-1 seropositive patients, followed by pneumocystis pneumonia and mycobacterial TB (88).

Neurological complications of the peripheral nervous system are common in HIV-1 infected adults. Peripheral neuropathy is the most common neuromuscular manifestation observed in HIV/AIDS. Furthermore, in the era of HAART, the prevalence has

increased. The causes include chronic HIV-1infection, termed HIV-associated distal sensory neuropathy (HIV-PN), and treatment-related toxicity termed antiretroviral toxic neuropathy (HIV-ATN). Less common peripheral neuropathies include autonomic neuropathy, acute and chronic inflammatory demyelinating polyneuropathies (AIDP and CIDP), polyneuropathy associated with DILS, toxic polyneuropathy and peripheral nervous system vasculitis (89).

The most common peripheral neuropathy in HIV-1 infection is HIV-PN and HIV-ATN. The frequency of HIV-PN increases with worsening immunosuppression. 35% of patients with moderate to severe immunosuppression ($CD4^+$ T lymphocyte count < 350 cells/ul) have a symptomatic peripheral neuropathy. After the introduction of HAART, multiple studies have suggested an increasing trend of peripheral neuropathies. This increase is felt to stem from the additive roles of antiretroviral toxic neuropathy in combination with decreased mortality rates and hence a growing population with peripheral neuropathies (89).

The dideoxynucleoside NRTIs include didanosine, zalcitabine and stavudine. These drugs have been associated with a 3-fold increase in risk for peripheral neuropathy in AIDS patients. The mechanism of neurotoxicity involves the inhibition of mitochondrial DNA gamma polymerase, a key enzyme for mitochondrial DNA replication and repair. The risk of antiretroviral toxic neuropathy increases with increasing age, drug dosage and duration, and the presence of pre-existing peripheral neuropathy, and generally occurs within the first year of treatment and most commonly within the first 3 months. Protease inhibitors such as indinavir, ritonavir and saquinavir may also result in neurotoxicity. It is not known whether this is due to direct neurotoxicity or from the consequences of metabolic derangements that result from the PIs (89).

HIV-1 seropositive adults are at increased risk of developing cancer, especially in the later stages of AIDS. Several neoplasms such as Kaposi's sarcoma, non-Hodgkin lymphoma and invasive cervical cancer occur with greater frequency in HIV-1 seropositive patients and are considered AIDS-defining malignancies (90). However, with the increased survival of HIV-1 seropositive patients on HAART or combination anti-retroviral therapy (cART), as shown by Couzigou, et al, 2007, an increased risk for non-AIDS defining cancers has been noted in this population group (91,92). Additionally, several studies have shown an increased incidence for many other types of cancers, including haematological malignancies such as Hodgkin lymphoma and MM (92,93). More specifically, an increased incidence for MM has been demonstrated in

HIV-1 seropositive patients (12,94-96). Not only does MM occur at a younger age in HIV-1 seropositive patients, but it also presents with more aggressive disease, more extramedullary disease with plasmacytomas and more atypical features, with a generally poorer outcome, compared to HIV seronegative MM (12,94-96).

1.9.9. Pathophysiology of Multiple Myeloma in HIV

Little is known about the mechanisms that drive plasma cell malignant transformation in HIV-1 seropositive patients, but chronic antigen stimulation and immunodeficiency are thought to be important factors (97). An increase in immunoglobulins in HIV-1infection is commonly seen. In most cases, the increase is polyclonal. However, a distinct but related phenomenon that is also observed is an oligoclonal or monoclonal band in HIV-1 seropositive patients (98,99).

Furthermore, patients with HIV/AIDS, have increased numbers of circulating immunoglobulin secreting cells. Marked abnormalities in B lymphocyte activation and immunoregulation directly at the level of the B lymphocyte as well as T lymphocyte control of B lymphocyte function have been demonstrated. This B lymphocyte hyperactivation, together with abnormal T lymphocyte regulation of B lymphocytes, co-existent Epstein Barr Virus (EBV) infection and elevated levels of IL-6, all contribute to chronic antigenic stimulation with a polyclonal gammopathy and ultimately culminating in a monoclonal gammopathy and plasma cell malignancy (100,101).

The hypergammaglobulinaemia as indicated above, was exemplified in the Italian study by Re et al, 1992 (101). Konrad et al, 1993, demonstrated an IgG kappa paraprotein directed against the HIV-1 p24 antigen, in a 30-year-old male, with HIV (99), while Cauda, et al, 1999, were able to show the beneficial effects of HAART, with a reduction in both the HIV viral load and monoclonal band in a 35 year old male, with MGUS and HIV (102).

1.9.10. HIV and Multiple Myeloma

HIV with its resultant immunodeficiency predisposes individuals to a variety of plasma cell disorders, including reactive bone marrow plasmacytosis, MGUS, plasmacytomas and MM (94). There are a number of studies of MM occurring in association with concurrent HIV-1 infection in the published medical literature.

Table 1.1 summarizes a number of studies of the association of MM with HIV. It includes a total of 13 studies: 6 from North America (United States of America – USA), 4 studies from

Africa (3 from South Africa and 1 from the Ivory Coast), 2 from Europe (1 each from France and Italy), and 1 from South America (Brazil) (7,12,94,95,97,102-109). In summary, HIV seropositive individuals with MM, compared to their seronegative counterparts, present at a younger age, with a less marked male predominance in some of the studies, more aggressive disease (as evidenced by a more advanced ISS stage etc.), more extramedullary disease (characterized by plasmacytomas) and a generally poorer outcome (7,12,94,95,97,102-109). See details in Table 1.1.

Table 1.1: Association of Multiple Myeloma (MM) with Human Immunodeficiency Virus (HIV) Infection

Number and reference	Title and authors and year of publication	Number and M:F ratio	Age (mean or median)	Salient clinical and laboratory features	Other comments
1 Ref: 103	Paraproteinemia, plasmacytoma, myeloma and HIV infection. Fiorino AS and Atac B. Leukemia.1997; 11:2150-2156	Reference made to various publications	33	Younger age at presentation. MGUS higher in HIV seropositive populations	General review of the literature USA
2 Ref: 104	Multiple myeloma in an HIV positive man presenting with primary cutaneous plasmacytomas and spinal cord compression. Lallemand F, et al. Journal of the American Academy of Dermatology. 1998;39:506-508	1 male	53	Cutaneous plasmacytomas. Spinal plasmacytoma. IgAκ MM. EBV +. Osteolytic bone lesions Treated with Melphalan and Prednisone. Died 3 weeks later	Atypical presentation. Primary skin involvement of plasmacytomas as erythemato-violaceous nodules. France
3 Ref: 105	Extramedullary plasmacytoma diagnosed in an HIV-positive patient by an unusual clinical presentation.de Camargo Moraes P, et al. Case Reports in Dentistry. 2016	1 male	44	Extramedullary plasmacytoma involving the palate, gums and maxilla. Later, expanding lesions (plasmacytomas) at L5/S1 vertebrae and progression to MM. CD4=20/ul. Treated with thalidomide, dexamethasone, radiation and pamidronate, with significant initial improvement. However, defaulted treatment and died of probable disease progression	Unsure whether the diagnosis is MM plasma-blastic NHL. Brazil
4 Ref: 106	Immunoglobulin A□ Multiple Myeloma in a patient with HIV: An unusual cause of massive ascites. Abdulsamad M, et al. Case Reports in Gastroenterology. 2017;11:201-206	1 female	48	Confusion. Ascites. Renal dysfunction. Anaemia. Stage III (ISS). IgAλ MM. Planned to receive treatment with bortezomib and dexamethasone	Unusual presentation with ascites. USA
5 Ref: 107	A retrospective analysis of ten symptomatic multiple myeloma patients with HIV infection: A potential therapeutic effect of HAART in multiple myeloma.Li G, et al. Leukemia Research. 2014;38:1079-1084	10 7 females 3 males M:F 0.33:1	50	Bone lesions - 60%. ISS stage (2 – I, 4 – II, 4 – III). 7/10 IgG, 1/10 IgA, 1 light chain κ, 1 non-secretory MM. 2 plasmacytomas. Treatment: 8 thalidomide based regimen. 3 changed to lenalidomide based regimen. 6 received ASCT	Inhibitory effect of HAART on the M-protein in HIV+ MM. Superior OS and PFS on HAART. USA
6 Ref: 97	Plasma cell disorders in HIV infected patients: epidemiology and molecular mechanisms.Coker WJ, et al. Biomarker Research. 2013;1:8	3 2 males 1 female M:F 2:1	52	58, female with polyclonal hypergammaglobulinemia with concomitant monoclonal gammopathy. Treated with HAART.	Different presentations of HIV and plasma cell disorders. USA

Number and reference	Title and authors and year of publication	Number and M:F ratio	Age (mean or median)	Salient clinical and laboratory features	Other comments
				45, male with background polyclonal gammopathy with MM. Treated with thalidomide and dexamethasone. 53, male with multiple OIs, lytic lesions with pathological fractures and plasmacytomas. Treated with bortezomib, cyclophosphamide and dexamethasone and radiotherapy, then changed to VRd and ASCT. Achieved CR	
7 Ref: 95	Concomitant HIV infection in newly diagnosed multiple myeloma patients is hard to recognise and should be tested for routinely in areas of high endemicity.de Groot JJB, et al. SAMJ;2017;107(9):781-787	89 49 males and 40 females 16 HIV+, M:F 3:1 73 HIV – M:F 1:1	51 HIV + 59 HIV -	12.5% HIV positivity rate. HIV seropositive patients: bone pain 100%, osteolytic lesions 73%, plasmacytomas 50%, vertebral body collapse 46%, pathological fractures 31%, ISS III 56%. Only IgG MM. CD4 212/ul.	Compared to HIV – MM, HIV + MM presented at a younger age, fewer lytic lesions, less renal impairment, lower neutrophil counts. South Africa
8 Ref: 108	Multiple Myeloma and Human Immunodeficiency Virus: Experience in Cote D'ivoire. Nanho CD, et al. Journal of Blood Research and Hematologic Diseases. 2019;4:1	10 6 males 4 females M:F 1.5:1	53	Bone pain 100%. Anaemia 100%. Pathological fractures 60%. Hypercalcaemia 60%. Renal failure 30%. ISS III 70%. Treatment: Thalidomide and dexamethasone 4/10, Chemotherapy 2/10, Chemotherapy and thalidomide 3/10, Thalidomide, melphalan and prednisone 1/10. CR 1/10, PR 5/10, VGPR 2/10, SD 1/10, PD 1/10	10 patients HIV + among 101 patients with MM. Prevalence 9.9%. Ivory Coast
9 Ref: 109	Thalidomide based treatment for HIV-associated multiple myeloma: a case report. Aboulafia DM. The AIDS Reader. 2003;13:383-389	1 male	45	IgG MM. Immuneparesis. Anaemia. Rash. Fever. Lymphadenopathy. Sore throat. Treated with ARVs, thalidomide, dexamethasone, clarithromycin and pamidronate. Benefit of thalidomide: relatively fewer side effects, safe, immunologic and disease related beneficial effects	Use of thalidomide.Rapid and dramatic antitumor response. USA

Number and reference	Title and authors and year of publication	Number and M:F ratio	Age (mean or median)	Salient clinical and laboratory features	Other comments
10 Ref: 7	An Epidemiological study of Multiple Myeloma in Southern Africa. Patel M. 2000. PhD thesis. University of the Witwatersrand	170 2 HIV+ 1 male 1 female M:F 1:1	45 61 (170 patients)	52, male. Extramedullary plasmacytoma of the buccal mucosa. Extensive osteolytic bone lesions. Bone marrow plasmacytosis 10%. CD4=90/ul. Non-secretory MM. Treated with dexamethasone and radiotherapy, with marked reduction in size of plasmacytoma. 38, female. Very severe anaemia. Hb=2.2 g/dl. IgGλMM. Paraprotein=51.5 g/l. Bone marrow plasmacytosis 14%.CD4=180/ul.Treatment: Blood transfusion, erythropoietin, melphalan and prednisone. Refractory anaemia despite above measures. Lost to follow up	2/170 HIV + patients = 1.17% prevalence. 170 patients reviewed between 1992 and 1997 at CHBAH. South Africa
11 Ref: 12	Multiple Myeloma at Chris Hani Baragwanath Academic Hospital. van der Walt AJ. MMed dissertation. University of the Witwatersrand. 2016	289 18 HIV+	45 HIV+ 58 (289 patients)	Compared to HIV- patients, HIV+ patients presented at a younger age, with more frequent plasmacytomas and less immunoparesis. No difference in survival between the seropositive and seronegative patients (but groups not comparable in terms of numbers)	13/289 patients = 6.2% prevalence. 289 patients reviewed between 1998 and 2010 at CHBAH. South Africa
12 Ref: 102	Beneficial effect of highly active antiretroviral therapy (HAART) in reducing both HIV viral load and monoclonal gammopathy. Cauda R, et al. European Journal of Haematology. 1999;63:134-135	35 males	35	IgGκ paraprotein. Raised ESR. No lytic lesions. 20% plasma cells on bone marrow biopsy. CD4=127/ul. Treated with HAART. Paraprotein decreased from 3.9 to 0.7 g/dl. Improvement in CD4 count to 480/ul and viral load to below detectable limits	Beneficial effect of HAART Italy
13 Ref: 94	Impact of HIV on clinical presentation and outcomes of individuals with Multiple Myeloma.Giri S, et al. Blood. 2018 (suppl) 3162	162 62 HIV+ (99.4% Male) 100 HIV-	59	Younger age at presentation. More disseminated disease and aggressive clinical course. Significantly higher rate of extramedullary disease. Inferior outcomes	Analysis of MM in the Veterans Aging Cohort Study (VACS). USA

1.9.11. Multiple Myeloma in Africa

A number of studies on MM have been described in the literature. Most of these studies are retrospective and have been reported from various countries, including Nigeria, Kenya and South Africa (7,12,95,110-121). The salient features in these studies have been included in Table 1.2. In summary, MM in patients from Africa share many similarities with MM described in the Western World. However, there are some noteworthy differences, which include the following:

a. Younger age group at presentation (5 – 10 years younger),
b. Late presentations, with more aggressive disease and more advanced stage disease,
c. Late referrals, with more acute complications (e.g. infection, renal impairment, hypercalcaemia, spinal cord compression etc.), which impacts negatively on patient outcomes, and
d. Less access to state of the art and novel therapies,
e. Poorer prognosis, outcomes and survival, as a result of the factors mentioned above (7,12,95,110-121).

Table 1.2: Studies of Multiple Myeloma (MM) in Africa

Number and reference	Title, authors and year of publication	Number of patients M:F ratio	Age (mean or median)	Clinical and laboratory features	Other comments	Country
1. Ref: 7	An Epidemiological study of Multiple Myeloma in Southern Africa. Patel M. 2000. PhD thesis. University of the Witwatersrand	170 101 males 69 female M:F ratio 1.45:1 1.2% HIV+	61 (170 patients) <40 years 7%	Bone pain 94%, Anaemia 81%, Infection 60%, Hypercalcaemia 39%, Osteolytic bone lesions 88%, Vertebral compression fractures 50%, Plasmacytoma 40%, PS≥2 70%, Stage III 75%, IgG 63%. OS 28 months, Median OS 15.5 months	1992-1997 CHBAH. Supportive care and conventional chemotherapy. Younger age. Late presentations with advanced stage disease. Less favourable outcome	South Africa
2 Ref: 110	Musculoskeletal presentation of Multiple Myeloma at General Hospital Douala, Cameroon. Doualla-Bija M, et al. East African Medical Journal. 2014;91:311-316	62 39 females 24 males M:F ratio 1:1.6	57 <40 years 6.5%	Bone pain 76%, Anaemia 71%, Osteolytic bone lesions 58%, Veterbral compression fractures 47%, Hypercalcaemia 26%, Renal dysfunction 18%. IgG 86%, Stage III 63%, HIV+ 2/62 (3%)	2007-2013 Douala General Hospital. Bone pain and anaemia – high index of suspicion for MM Female predominance (63%) unusual	Cameroon
3 Ref: 111	Multiple Myeloma: a descriptive study of 217 Egyptian patients. El Husseiny NM, et al. Ann Haematol. 2014;93:141-145	217 129 males 89 females M:F ratio 1.45:1	59 <40 years 4%	Anaemia 95%, Bone pain 70%, Hypercalcaemia 40%, Renal dysfunction 30%, IgG 73%. Median OS 38 months	Kasr Al Aini Hospital 2000-2010	Egypt
4 Ref: 112	A review of 74 patients with newly diagnosed multiple myeloma at a tertiary referral hospital in Nairobi, Kenya. Kiraka G, et al. J Afr Cancer. 2014;6:70-74	74 39 males 35 females M:F ratio 1.12:1	59 <40 years 5%	Bone pain 76%, Osteolytic bone lesions 62%, Renal dysfunction 52%,Anaemia 47%, Vertebral compression fractures 38%, Hypercalcaemia 34%, Infections 16%, IgG 50%	Aga Khan University Hospital 1999-2011	Kenya
5. Ref: 113	Multiple myeloma in Nigeria: An insight to the clinical, laboratory features and outcomes. Madu AJ, et al. Nigerian Journal of Clinical Practice. 2014;17:212-217	32 17 males 15 females M:F ratio 1.15:1	62	Bone pain 78%, Anaemia 72%, Osteolytic bone lesions 73%, Pathological fractures 69%, IgA 46%	2002-2012 University of Nigeria Teaching Hospital, Enugru. Higher proportion of IgA MM. Treatments: M, MP, MPT, CVAP, Bortezomib based	Nigeria
6. Ref: 114	Multiple myeloma in Nigeria: a multicenter epidemiological and biomedical study. Odunukwe NN, et al. Pan African Medical Journal. 2015;22:292	135 70 males 65 females M:F ratio 1.1:1	60 <40 years 5%	Anaemia 77%, Bone pain 74%, Pathological fractures 44%, Renal dysfunction 36%.	Data from 8 tertiary institutions in Nigeria 2005-2014. Treatment included: MP 49%, MPT 31%, Bortezomib based 14%. Median survival 7.4 months	Nigeria
7. Ref: 115	Multiple myeloma: The burden and clinico-laboratory	21 11 males	60	Bone pain 96%, Osteolytic bone lesions 86%, Renal dysfunction 19%, IgG 70%	University College Hospital, Ibadan 2007-2012. Unusual	Nigeria

Number and reference	Title, authors and year of publication	Number of patients M:F ratio	Age (mean or median)	Clinical and laboratory features	Other comments	Country
	characteristics in a Nigerian foremost tertiary Hospital. Olaniyi JA and Fowodu FO. J Appl Haematol. 2015;15:58-63	10 females M:F ratio 1.1:1			finding of no hypercalcaemia. Treatment MP and MPT	
8. Ref: 116	Clinical and Radiological Features of Multiple Myeloma patients at the University Teaching Hospital, Lusaka, Zambia. Mwaba F, et al. Medical Journal of Zambia. 2016;43:7-11	46 25 males 21 females M:F ratio 1.2:1	53	Osteolytic bone lesions 65%, Backache 59%, Bone pain 46%, Anaemia 30%, Pathological fractures 26%, Hypercalcaemia 11%	2008-2015 University Teaching Hospital Osteolytic bone lesions most common	Zambia
9. Ref: 12	Multiple Myeloma at Chris Hani Baragwanath Academic Hospital. van der Walt AJ. MMed dissertation. University of the Witwatersrand. 2016	289 145 males 144 females M:F ratio 1:1	58	Anaemia 92%, Bone pain 87%, Osteolytic bone lesions 90%,Vertebral compression fractures 43%, Stage III ISS 57%, Hypercalcaemia 35%, Renal dysfunction 32%, Plasmacytomas 18%. IgG 55%	1998 -2010 CHBAH. 18 HIV+ (6.2%). Median OS 15.9 months	South Africa
10. Ref: 95	Concomitant HIV infection in newly diagnosed multiple myeloma patients is hard to recognize and should be tested for routinely in areas of high endemicity.de Groot JJB, et al. SAMJ;2017;107(9):781-787	89 49 males 40 females 16 HIV+, M:F 3:1 73 HIV – M:F 1:1	51 HIV + 59 HIV -	HIV-: Bone pain 90%, Osteolytic bone lesions 93%, Plasmacytoma 26%, Vertebral collapse 44%, Pathological fractures 27%. Stage III ISS 58%. IgG MM 71% HIV+: Bone pain 100%, Osteolytic bone lesions 74%, Plasmacytoma 50%, Vertebral collapse 47%, Pathological fractures 31%. Stage III ISS 56%. IgG MM 100%	16 HIV+ (12.5%). Universitas Hospital, Bloemfontein	South Africa
11. Ref: 117	Multiple myeloma in Niger Delta, Nigeria: complications and the outcome of palliative interventions. Nwakubo OC, et al. Cancer Management and Research. 2017;9:189-196	26 18 males 8 females M:F ratio 2.3:1	63 <40 years 7%	Bone pain 85%, Osteolytic bone lesions 70%, Anaemia 62%, Renal dysfunction 23%, Stage III 62%, IgG 75%	10 tear multicenter study at 3 centres 2003-2012 Late diagnosis. Inadequate palliative care. Mean OS 39.7 months. 5 year survival 7.6%	Nigeria
12. Ref: 118	Presentation and survival of multiple myeloma patients in Ghana. Acquah ME, et al. Ghana Med J. 2019;53:52-58	169 87 males 82 females M:F ratio 1.1:1	58	Bone pain 96%, Osteolytic bone lesions 76%, Anaemia 67%, Pathological fractures 44%, Hypercalcaemia 36%, Renal dysfunction 35%. ISS stage III 51%	2002-2016 Ghanaian tertiary hospital. Treatments: MP, MPT, VAD-T, CTD, Thalidomide-dexamethasone (Thal-dex.)	Ghana

Number and reference	Title, authors and year of publication	Number of patients M:F ratio	Age (mean or median)	Clinical and laboratory features	Other comments	Country
					Median survival 33 months	
13. Ref: 119	A review of diagnostic features of multiple myeloma Sub-Saharan black subjects Africa. Tatnou DMK and Francoise NS. Abstract. 17th International Myeloma Workshop. 2019.e229	1417	58	Bone pain 72-75%, Anaemia 47-85%, Renal dysfunction 18-20%, IgG 48%. Most patients, stage III disease	Cochrane review – 21 studies; 1417 individuals 1985-2017 Younger patients, more advanced stage disease Mainstay of treatment: MP	Cameroon
14. Ref: 120	Retrospective analysis of presentation, treatment and outcomes of Multiple Myeloma at a large public referral hospital in Eldoret, Kenya. Manyega KM, et al. JCO Global Oncology. 2021;7:391-399	221 124 males 97 females M:F ratio 1.3:1	61	Bone pain 70%, Osteolytic bone lesions 59%, Hypercalcaemia 55%, Anaemia 47%, Pathological fractures 29%, Spinal cord compression 29%, Renal dysfunction 14%	2009-9019 Moi Teaching Referral Hospital. Treatments; Thal-dex 65%, BTD 15%, MP 12% OS – 1year 70%, 5 years 21%. Median OS 29 months	Kenya
15. Ref: 121	Characteristics and outcomes of patients with multiple myeloma at the Uganda Cancer Institute. Okello CD, et al. African Health Sciences. 2021;21:67-74	217 119 males 98 females M:F ratio 1.2:1	59	Bone pain 84%, Osteolytic bone lesions 69%, Stage III ISS 70%, IgG 72%. Median OS 30 months	2008-2012 Uganda Cancer Institute HIV+ 12/197 (6%). Treatments: MP, MPT, VAD, Thal-dex, Bortezomib based	Uganda

1.9.12. Plasmablastic lymphoma (PBL) mimicking Multiple Myeloma (MM)

Plasmablastic non-Hodgkin lymphoma (NHL) is a relatively new entity, first described by Delecluse, et al, in 1997 (122). It is an aggressive B-cell NHL, typically presenting in young individuals, at extra-nodal sites (such as the oral, sino-nasal and anal cavity) and frequently associated with immunosuppression, classically with HIV, in the local South African context (122-124). However, in elderly HIV sero-negative patients, the disease manifests more typically, with predominantly nodal and extranodal disease (122).

In the current HIV era, with the increase in patients with Plasmablastic NHL in South Africa, a study of this nature would be incomplete, if no mention is made of HIV associated Plasmablastic NHL mimicking HIV-associated MM, as there may be a number of overlapping features between the two entities, such as HIV sero-positivity, younger age at presentation, oral cavity masses, plasmablastic differentiation on morphology and plasma cell marker positivity etc. (8,123,124). Table 1.3 highlights in greater detail, the differences between PBL and MM. This differentiating tool may be relevant and very useful for the treating clinician, who is faced with a diagnostic dilemma and needs to separate out these two entities. However, despite this, clinicians still encounter the odd ‘grey’ patient, where there may be a number of overlapping features, without a clear demarcation between these two conditions.

Table 1.3: Differences between PBL and MM

	MULTIPLE MYELOMA	**PLASMABLASTIC LYMPHOMA**
Epidemiology and Demographics	Higher incidence. Median age 55-65 years (up to 70 years in the Western world); <2-7% under 40 years; M > F (1-1.5:1)	Lower incidence (high in areas of HIV seroprevalence); Mostly occurs in young individuals (38-41 years) with HIV+; May occur in the elderly - M=F or F > M (1-1.2:1)
Clinical features	Bone disease, infection, renal impairment, extramedullary involvement (plasmacytomas), cytopenias etc.	'B symptoms', HIV seropositive present predominantly with extranodal disease (oral, sino-nasal, anal cavity), other extranodal sites including bone, skin, GIT etc., lymphadenopathy uncommon – more typical in the elderly
HIV status	Up to 10-15% positive	>90% positive
Paraprotein in serum and urine	Very common	Rare, but may be detected
Bone disease	Very common	Uncommon. Bone disease including osteolytic bone disease and pathological fractures may occur
Extranodal /Extramedullary disease	Plasmacytoma	Lymphoma .. oral/sino-nasal cavity, anal cavity, other
Bone marrow	Plasmacytosis – prominent, atypical, clonal	Plasmacytosis less common
Histology	Plasmacytoma with kappa or Lamba LC restriction, plasma cell markers, CD 56 + Ki -67 30-60%	Aggressive plasmablastic morphology; plasma cell markers; CD 56-; Ki-67 > 70-90%
Cytogenetics; EBER-ISH	17p: t(14:16); t(14:20); t(11:14), 13q14; t(4:14), hyperdiploidy, chromosome 1 abnormalities, complex etc. EBER-ISH negative; P-53; C-MYC, BRAF, etc.	Non-specific; EBER-ISH positive: C-MYC abbreviations, PRDM1 etc.
Disease behavior	Indolent, generally less aggressive	Aggressive, high grade
Treatment	More defined: better overall prognosis. Supportive care including antiretroviral therapy Specific treatment – various combinations of chemotherapy, corticosteroids, immunomodulatory agents, proteasome inhibitors and monoclonal antibodies as induction, consolidation with ASCT in transplant eligible patients and maintenance therapy Other modalities – radiotherapy , surgery, cellular therapies etc.	Not clearly defined, poor prognosis especially with relapsed, refractory disease Supportive care including antiretroviral therapy Specific treatment – combination chemotherapy (e.g. CHOEP, EPOC, R-EPOC, CDE etc.), addition of proteasome inhibitors such as bortezomib or monoclonal antibodies such as daratumomab Role of ASCT unclear Other modalities – radiotherapy, surgery, experimental

2.0. CHAPTER 2: PATIENTS AND METHODS

2.1. AIM OF THE STUDY

The aim of the study was to retrospectively describe the demographic profile and clinical presentation of HIV-1 sero-positive patients with Multiple Myeloma (MM), who presented and were/are being managed at the Clinical Haematology Unit, Department of Medicine, CHBAH, during the period 1/1/2006 to 31/12/2020 (15 years).

2.2. OBJECTIVES OF THE STUDY

i) To describe the demographic profile of HIV-1 sero-positive patients diagnosed with MM,

ii) To describe the clinical findings, laboratory parameters, staging and radiological imaging at presentation, and

iii) To describe the treatment response, complications and outcome of the patients.

2.3. PATIENTSAND METHODS

2.3.1. Study design

The study is a retrospective, descriptive study with comparative elements.

2.3.2. Study population

This is a single-center retrospective study conducted at the Clinical Haematology Unit, Department of Medicine, CHBAH. CHBAH is a tertiary, public sector hospital, based in Soweto, Johannesburg, South Africa and serves as a teaching hospital, affiliated to the University of the Witwatersrand academic complex. A register/database created by the Clinical Haematology Unit was used to identify all the patients that had been documented to have HIV-1 positive serology and a diagnosis of MM during the period 1/01/2006 to 31/12/2020. Patient records were retrieved from the archives at the Clinical Haematology Unit and the laboratory results from the National Health Laboratory Services (NHLS) website.

2.3.3. Inclusion criteria

a. Adults ≥ 18 years of age

b. Confirmed diagnosis of HIV-1 infection in association with MM

c. Patients diagnosed and treated during the period 1/01/2006 to 31/12/2020

2.3.4. Exclusion criteria

a. Patients with inadequate and incomplete records (including clinical and laboratory information as well as therapeutic and follow up outcome information)

The total number of patients who were HIV-1 sero-positive, together with MM during the study period was 84. Of these 84 patients, 70 were included and 14 were excluded. In 11/14 patients who were excluded, the files were not found, as these patients may have died before a file could be opened, precluding documentation of relevant patient information. It is also possible that some of these files may have been misplaced. In 3/14 patients, there was inadequate or incomplete information in the patient's files. As such, they were excluded from the study.

2.4. CONFOUNDING VARIABLES AND LIMITATIONS

Due to the retrospective nature of the study, some data was incomplete or missing. There were also several patients who were lost to follow up/non-compliant or who died shortly after the diagnosis of MM was made, resulting in incomplete or missing data, as indicated above.

2.5. DATA COLLECTION

Data was obtained retrospectively from the patient files and captured onto a data sheet (see appendices F and G). Prior to analysis, the data was checked and entered into a Microsoft Excel spread sheet.

2.6. SAMPLE SIZE

A total of 70 patients were evaluable for inclusion in the study. 14 patients were excluded (17%). The total number of MM patients diagnosed during this time period was 601. Therefore, the HIV sero-positive cohort represents 18% of the total MM population seen in the 15-year study period.

2.7. ETHICS APPROVAL

Ethics approval was obtained from the Human Research Ethics Committee (HREC) of the University of the Witwatersrand, Johannesburg. Consent for the use of patient records was obtained from the Head of the Clinical Haematology Unit, Department of Medicine, the Academic Head of the Department of Internal Medicine, and the CEO of CHBAH. Consent

was also obtained from the NHLS to review appropriate laboratory data from the patients included in the study. Patient identifiers were not used on the data sheet but instead kept separately by the investigator to maintain patient anonymity and confidentiality. Patient information and raw data were accessible to the study investigator, supervisors and statistician. The study was commenced upon obtaining permission and approval from all the above-mentioned authorities.

Additional ethics clearance was requested (to extend the study period by 2 years, to include 2019 and 2020), in order to achieve the desired number of patients (i.e.> 50 patients). This was granted by the HREC (see Appendices A and B).

2.8. STATISTICAL ANALYSIS

Statistical analysis was performed using the program Stata Version 17. The patient demographics were summarized using descriptive statistics for dependent variables that are normally distributed, including means and standard deviations. A Student t-test was used to compare normally distributed variables and the Mann-Whitney or Kruskal-Wallis test was used for data that is not normally distributed.

Time-to-event analysis (survival analysis) was used to estimate survival in HIV-1 sero-positive patients with MM. Time started at diagnosis and ended at date of death for patients who died, or last date of contact for patients who were still alive at last date of contact. Kaplan Meier (KM) survival curves were used to estimate overall survival, and survival by CD4 count, definitive treatment (chemotherapy and/or radiation therapy), disease stage and response to chemotherapy. The Log rank test for equality of survivor functions was used to test for statistical differences by CD4 count, treatment, and disease stage. For the purpose of statistical analysis, a 95% confidence interval, with a p-value ($p<0.05$) was considered significant.

3.0. CHAPTER 3: RESULTS

3.1. DEMOGRAPHIC FINDINGS

During the study period (01/01/2006 to 31/12/2020 – 15 years), a total of 601 patients were diagnosed with MM. Furthermore, 84 patients were HIV-1 seropositive (14%). Of these 84 patients, 14 were excluded (see chapter 2.0 for details). A total of 70 evaluable HIV-1 seropositive patients were included in this study (12%). Of these 70 patients, there were 42 females and 28 males with a female to male ratio of 1.5:1. The mean age for females was 49.9 years (range 31-77 years), and males was 50.6 years (range 36-73 years), while the mean age for the whole group was 50.2 years (range 31-77years).

All the patients in the study were of Black African ethnicity, in keeping with the demographic of CHBAH, where >90% of the patients admitted to the hospital are of Black African ethnicity. The total number of patients diagnosed per year is depicted in Figure 3.1. graphically and numerically in Table 3.1, below. It is clear from the data provided in Table 3.1, that the number of MM patients was stable in the first ten years of this study (01/01/2006 to 31/12/2015), with an HIV-1 seropositive rate of approximately 10-11%. However, in the latter five years of the study (01/01/2016 to 31/12/2020), the total number of MM patients increased by approximately 60% and the HIV-1 seropositive rate increased to 18%. This is noteworthy, given the ongoing impact of HIV on the lymphoproliferative disorders, including MM.

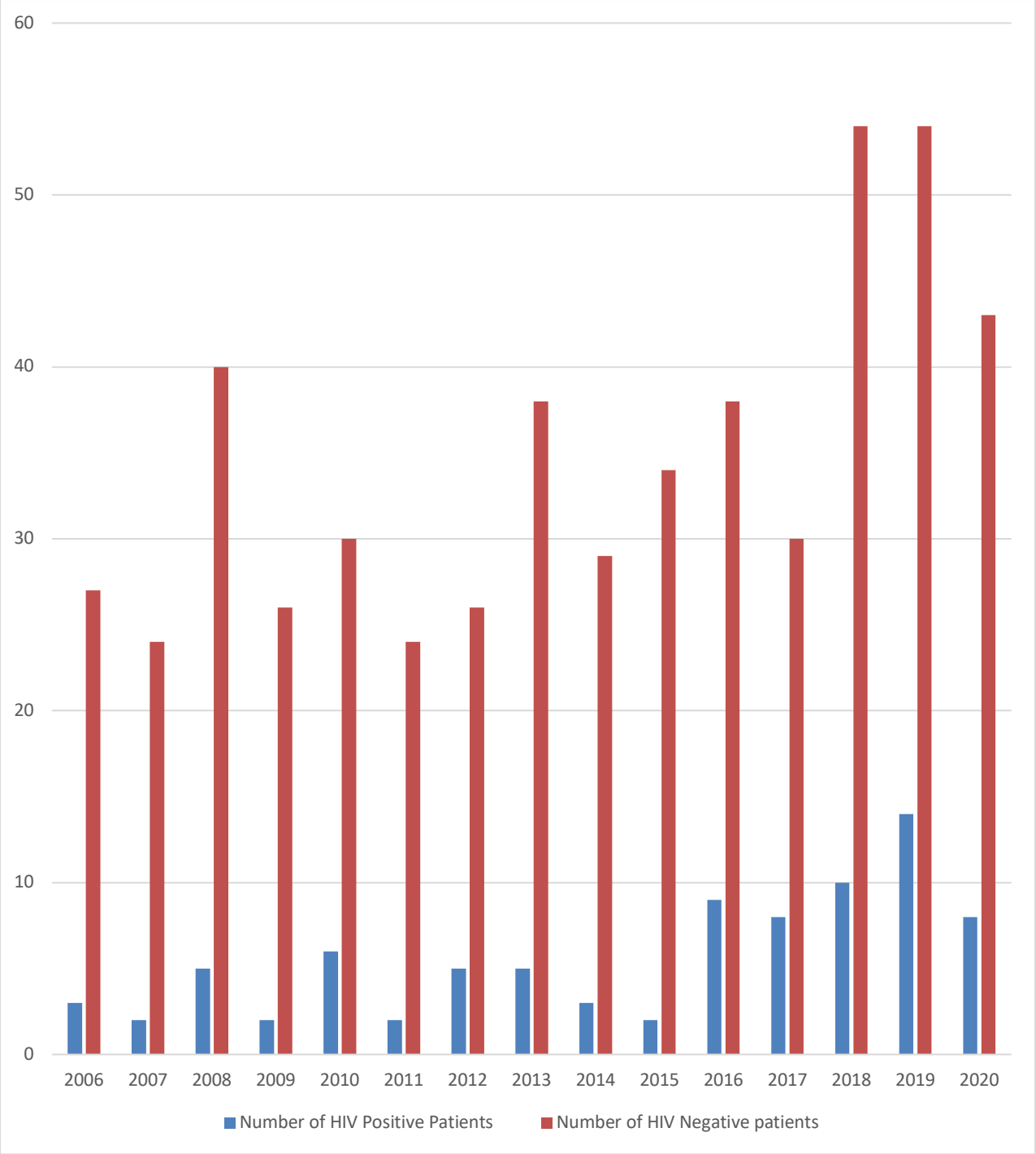


Figure 3.1: Total number of patients with Multiple Myeloma during the study period - 2006 to 2020

HIV: Human Immunodeficiency Virus Infection

Table 3.1: Total number of patients with Multiple Myeloma during the study period – 2006 to 2020

YEAR OF STUDY	HIV SEROPOSITIVE	HIV SERONEGATIVE	TOTAL NUMBER
2006	3	27	30
2007	2	24	26
2008	5	40	45
2009	2	26	28
2010	6	30	36
2011	2	24	26
2012	5	26	31
2013	5	38	43
2014	3	29	32
2015	2	34	36
2016	9	38	47
2017	8	30	38
2018	10	54	64
2019	14	54	68
2020	8	43	51
TOTAL	84	517	601 (13.97%)
1ST FIVE YEARS	18	147	165 (10.9%)
2ND FIVE YEARS	17	151	168 (10.11%)
3RD FIVE YEARS	49	219	268 (18.28%)

3.2. CLINICAL FINDINGS

The most common clinical findings at presentation are shown in Table 3.2. Bone pain was the most frequently reported symptom (79%), and pallor, the most common physical sign (48%). Strangely, weight loss was documented in 77% of the patients (more likely attributable to the HIV, at it is an uncommon feature of MM). Additionally, clinical evidence of plasmacytoma and neurological signs were evident in 29% and 28% of the patients, respectively.

Table 3.2: Clinical features in Human-Immunodeficiency-Virus-1 seropositive patients with Multiple Myeloma

Symptoms and signs	**Number**	**Percentage**
Bone pain	52 (66)	79%
Night sweats	14 (63)	22%
Loss of weight	50 (65)	77%
Fatigue	35 (64)	55%
History of bleeding	13 (66)	20%
Hyperviscosity	1 (65)	2%
Pallor	32 (66)	48%
Pedal oedema	6 (65)	9%
Clinically evident bleeding (ecchymosis, purpura, petechiae, haematemesis, active bleeding)	8 (67)	12%
Infection	4 (67)	6%
Clinically evident plasmacytoma	20 (68)	29%
Radiculopathy/Spinal cord involvement/ Paraparesis/ Paraplegia	19 (67)	28%

The ECOG (Eastern Co-operative Oncology Group) performance status (PS) of the patients is detailed in Table 3.3 below. Of note, 54.7% of the patients had a PS ≥2, while 45.3% had a good PS of <2, at presentation.

Table 3.3: Performance status in Human-Immunodeficiency-Virus-1 seropositive patients with Multiple Myeloma

Performance status (ECOG)	**Number**	**Percentage**
0	9 (64)	14%
1	20 (64)	31.3%
2	11 (64)	17.2%
3	13 (64)	20.3%
4	11 (64)	17.2%

With regard to the association of Tuberculosis (TB) in this study cohort, 19% had a past history of TB, 1% had a simultaneous new diagnosis of TB, at the time of the diagnosis of MM, and 3% developed TB during the follow up course of their disease. This is depicted in Table 3.4 below.

Table 3.4: Past or current diagnosis of TB in Human-Immunodeficiency-Virus-1 seropositive patients with Multiple Myeloma

Tuberculosis co-infection	**Number**	**Percentage**
At time of MM diagnosis	1 (70)	1.4%
Prior to MM diagnosis	13 (70)	18.6%
Patients diagnosed with TB during the course of the disease (i.e. during follow up of MM)	2 (70)	2.8%

3.3. LABORATORY FINDINGS

The laboratory findings at presentation are shown in Tables 3.5 to 3.10 below.

The mean haemoglobin (Hb) was 8.78 g/dl, with a range of 3-17.9 g/dl. Anaemia was evident in 86% of the patients, with mild / ≥ grade1 anaemia (Hb <11 g/dl) being present in 77% of the patients. The mean cell volume (MCV) was normocytic in 69%, microcytic in 7% and macrocytic in 24% of the patients, respectively.

The mean white cell count (WCC) was 6.65 x 10^9/l, with a range of 1.56 to 18.8 x 10^9/l. Leucopenia was present in 12% and leucocytosis in 7% of the patients. The mean lymphocyte count was 1.99 x 10^9/l, with a range of 0.09 to 6.28 x 10^9/l. Lymphopenia was evident in 23% and lymphocytosis in 4% of the patients, respectively. The mean neutrophil count was 3.9 x 10^9/l, with a range of 0.04 to 12.2 x 10^9/l. Neutropenia of varying grades was present in 16.5% of the patients, while netrophilia was present in 9% of the study patients.

The mean platelet count was 230 x 10^9/l. Clinical thrombocytopenia (platelet count <100 x 10^9/l) was seen 13%, while 'clear-cut' thrombocytosis was evident in 6% of the patients.

Table 3.5: Full blood count

Haemoglobin g/dl		**Number**	**Percentage**
Mean (range)	8.78 (3-17.9)		
No anaemia (Females)	≥12	5 (70)	7%
No anaemia (Males)	≥13	5 (70)	7%
Borderline/Grade 0 anaemia (Females)	11 to <12	2 (70)	3%
Borderline/Grade 0 anaemia (Males)	11- to <13	4 (70)	6%
Mild/Grade 1 anaemia	9.5 to <11	7 (70)	10%
Moderate/Grade 2 anaemia	8 to < 9.5	14 (70)	20%
Severe/Grade 3 anaemia	6.5 to < 8	20 (70)	29%
Very severe/Grade 4 anaemia	< 6.5	13 (70)	18%
Mean cell volume (MCV) fl			
Mean (range)	94 (73-122)		
Normal	80-100	47 (68)	69%
Microcytosis	<80	5 (68)	7%
Macrocytosis	>100	16 (68)	24%

White cell count x 10^9/l		**Number**	**Percentage**
Mean (range)	6.65 (1.56-18.8)		
Normal	4-11	56 (69)	81%
Leucopenia	<4	8 (69)	12%
Leucocytosis	>11	5 (69)	7%
Lymphocyte count x 10^9/l			
Mean (range)	1.99 (0.09-6.28)		
Normal	1-4	48 (66)	73%
Lymphopenia	<1	15 (66)	23%
Lymphocytosis	>4	3 (66)	4%
Neutrophil count x 10^9/l			
Mean (range)	3.9 (0.04-12.2)		
Normal	2 to 7.5	49 (66)	74.5%
Grade 1 neutropenia	1.5 to <2	2 (66)	3%
Grade 2 neutropenia	1 to <1.5	6 (66)	9%
Grade 3 neutropenia	0.5 to <1	1 (66)	1.5%
Grade 4 neutropenia	<0.5	2 (66)	3%
Neutrophilia	>7.5	6 (66)	9%
Platelet count x 10^9/l			
Mean (range)	230 (7-669)		
Normal	>150 to 400	45 (69)	65%
Borderline/Grade 0 thrombocytopenia	>100 to 150	8 (69)	12%
Grade 1 thrombocytopenia	>75 to <100	2 (69)	3%
Grade 2 thrombocytopenia	>50 to <75	0 (69)	0%
Grade 3 thrombocytopenia	>25 to <50	4 (69)	6%
Grade 4 thrombocytopenia	<25	3 (69)	4%
Borderline thrombocytosis	>400 to 450	3 (69)	4%
'Clear-cut' thrombocytosis	>450	4 (69)	6%

Table 3.6: CD4 counts

CD^+4 count cells/ul	**Number**	**Percentage**	
Mean (Range)	367 (23-964)		
<50	3 (65)	4.6%	$CD^+4 < 50$: 4.6%
50-100	5 (65)	7.7%	$CD^+4 \leq 100$: 12.3%
101-199	9 (65)	13.8%	$CD^+4 < 200$: 26.1%
200-349	15 (65)	23.1%	$CD^+4 < 350$: 49.2%
350-499	18 (65)	27.7%	$CD^+4 < 500$: 76.9%
≥500	15 (65)	23.1%	

The mean CD4 count was 367 cells/ul, with a range of 23-964 cells/ul. The CD4 count was <200 cells/ul in 26.1% of the patients, while 76.9% had a CD4 count of <500 cells/ul. A CD4 count of <50 cells/ul was only seen in 4.6% of the study patients.

Table 3.7: Biochemistry results

Vitamin B12 pmol/l		**Number**	**Percentage**
Mean (range)	538 (106-1881)		
	<145	0 (52)	0%
	145-637	38 (52)	73%
	637<1000	8 (52)	15%
	>1000	6 (52)	12%
LDH U/L			
Mean (range)	487 (100-4079)		
Normal	Up to 200	8 (56)	14%
Increased	>200	48 (56)	86%
Uric Acid mmol/l			
Mean (range)	0.42 (0.08-0.99)		
Normal (female)	0 -0.35	18 (56)	32%
Normal (male)	0 -0.45	12 (56)	21%
Elevated (female)	>0.35	16 (56)	29%
Elevated (male)	>0.45	10 (56)	18%
Corrected calcium mmol/l			
Mean (range)	2.8 (2.02-4.03)		
Low	< 2,05	1 (69)	2%
Normal	2.05-2.56	29 (69)	42%
Borderline	> 2.56 to 2.75	11 (69)	16%
Mild increase	> 2.75 to 3	11 (69)	16%
Moderate increase	> 3 to 3.5	5 (69)	7%
Severe increase	> 3.5	12 (69)	17%
Sodium mmol/l			
Mean (range)	135 (109-161)		
Normal	135-145	34 (68)	50%
Hyponatraemia	<135	32 (68)	47%
Hypernatraemia	>145	2 (68)	3%
Urea mmol/l			
Mean (range)	11.4 (1.6-42.7)		
Normal	2.6-7	36 (69)	52%
Elevated	>7	32 (69)	46%
Decreased	<2.6	1 (69)	2%
Creatinine umol/l			
Mean (range)	296 (40-1954)		
Low	<60	10 (69)	14%
Normal	60-120	28 (69)	41%
Elevated	>120 to 177	8 (69)	12%
Elevated	>177	23 (69)	33%
Total protein g/l			
Mean (range)	94 (49-153)		
Normal	60 to 85	23 (68)	34%
Decreased	<60	3 (68)	4%
Elevated	>85	42 (68)	62%
Globulin gap g/l			
Mean (range)	63 (17-136)		
Normal	20 to 40	17 (68)	25%

		Number	Percentage
Decreased	<20	2 (68)	3%
Elevated	>40	49 (68)	72%
Albumin g/l			
Mean (Range)	32 (13-47)		
Normal	35 to 50	24 (68)	35%
Decreased	<35	44 (68)	65%
ALP U/L			
Mean (range)	141 (29-482)		
Normal	Up to 120	37 (65)	57%
Elevated	>120	28 (65)	43%
B2M mg/L			
Mean (range)	14.5 (2.3-66.4)		
Decreased	<0.7	0 (54)	0%
Normal	0.7-1.8	2 (54)	3.7%
Elevated	>1.8 to <3.5	8 (54)	14.8%
Elevated	3.5 to 5.5	6 (54)	11.1%
Elevated	>5.5	38 (54)	70.4%

Table 3.7 depicts the biochemistry results in the study patients. Interestingly, the mean vitamin B12 level was 538 pmol/l, with a range of 106 to 1881 pmol/l. No patients had low vitamin B12 levels.

The mean LDH was 487 U/L, with a range of 100 to 4079 U/L. The LDH level was elevated in 86% of the patients.

The mean uric acid level was 0.42 mmol/l, with a range of 0.08 to 0.99 mmol/l. The uric acid was elevated in 29% of females and 18% of males, respectively.

The mean corrected calcium level was 2.8 mmol/l, with a range of 2.02 to 4.03 mmol/l. Hypocalcaemia was evident in only 2% of the patients, while hypercalcaemia was present in 56% of the patients, with a level of >2.75 mmol/l being present in 40% of the patients at presentation.

The mean sodium level was 135 mmol/l, with a range of 109 to 161 mmol/l. Hyponatraemia was present in 47% of the study population.

The mean urea level was 11.4 mmol/l, with a range of 1.6 to 42.7 mmol/l. An elevated urea level was found in 46% of the patients. With regard to the serum creatinine, the mean value was 296 umol/l, with a range of 40 to 1954 umol/l. Furthermore, 45% of the patients had an elevated creatinine level, with 33% of the patients having a creatinine level above 177umol/l.

The mean total protein level was 94 g/l, with a range of 49 to 153 g/l. An elevated total protein was seen in 62% of the patients. On further analysis of the total protein levels, the globulin fraction was elevated in 72% of the patients. The mean globulin level was 63 g/l, with a range of 17 to 136 g/l. Conversely, the mean albumin level was 32 g/l, with a range of 13-47 g/l. Hypoalbuminaemia was present in 65% of the patients at presentation.

The mean alkaline phosphatase level was 141 U/L, with a range of 29 to 482 U/L. An elevated alkaline phosphatase level was present in 43% of the patients.

The mean Beta 2 microglobulin (B2M) level was 14.5 mg/L, with a range of 2.3 to 66.4 mg/L. The B2M was elevated in vast majority of patients (96.3%), with levels ≥3.5 mg/L in 81.5% and >5.5 mg/L in 70.4%, respectively.

An M-protein (paraprotein) was present in 92.2% of the patients, as indicated in Table 3.8 below. In approximately half of the patients (48.5%), the paraprotein level was >30 g/l.

Table 3.9 shows the serum free light chain results. Kappa light chains were detected in 73% of the patients, while lambda light chains were evident in 55%, with an abnormal serum free light chain ratio being present in 49% of the study population.

Table 3.8: Serum M-protein levels

Serum M-protein g/l		**Number**	**Percentage**
Mean (range)	31 (2-93.1)		
No paraprotein detected		5 (64)	7.8%
	1 to 5	6 (64)	9.4%
	>5 to 10	3 (64)	4.7%
	>10 to 20	11 (64)	17.1%
	>20 to 30	8 (64)	12.5%
	>30 to 40	9 (64)	14.1%
	>40 to 50	12 (64)	18.8%
	>50	10 (64)	15.6%

Table 3.9: Serum free light chains

Serum free light chain - Kappa mg/l		**Number**	**Percentage**
Mean (range)	6831 (3.9-268 000)		
Decreased	<3.3	0 (49)	0%
Normal	3.3-19.4	13 (49)	27%
Elevated	>19.4	36 (49)	73%
Serum free light chain - Lambda mg/l			
Mean (range)	2533 (5.5-48900)		
Decreased	<5.7	1 (49)	2%
Normal	5.7 to 26.3	21 (49)	43%
Elevated	>26.3	27 (49)	55%
Serum free light chain ratio			
Decreased	<0.25	16 (49)	33%
Normal	0.25 to 1.65	9 (49)	18%
Elevated	>1.65	24 (49)	49%

Table 3.10 shows the different MM isotypes. IgG isotype was the most common (74.2%), with 46.6% of the patients having an IgG kappa and 27.6% having an IgG lambda isotype, respectively. IgA MM was the second most common isotype (17.3%), followed by light chain only MM (3.4%). Non-secretory MM was present in only 3.4% of the patients in this study.

Table 3.10: Subtype (Isotype) of Multiple Myeloma

Multiple Myeloma type	**Number**	**Percentage**
IgG kappa	27 (58)	46.6%
IgG lambda	16 (58)	27.6%
IgA kappa	7 (58)	12.1%
IgA lambda	3 (58)	5.2%
Light chain myeloma – kappa	2 (58)	3.4%
Light chain myeloma – lambda	0 (58)	0%
Non-secretory myeloma	2 (58)	3.4%
Negative serum M protein, without urine results available	1 (58)	1.7%

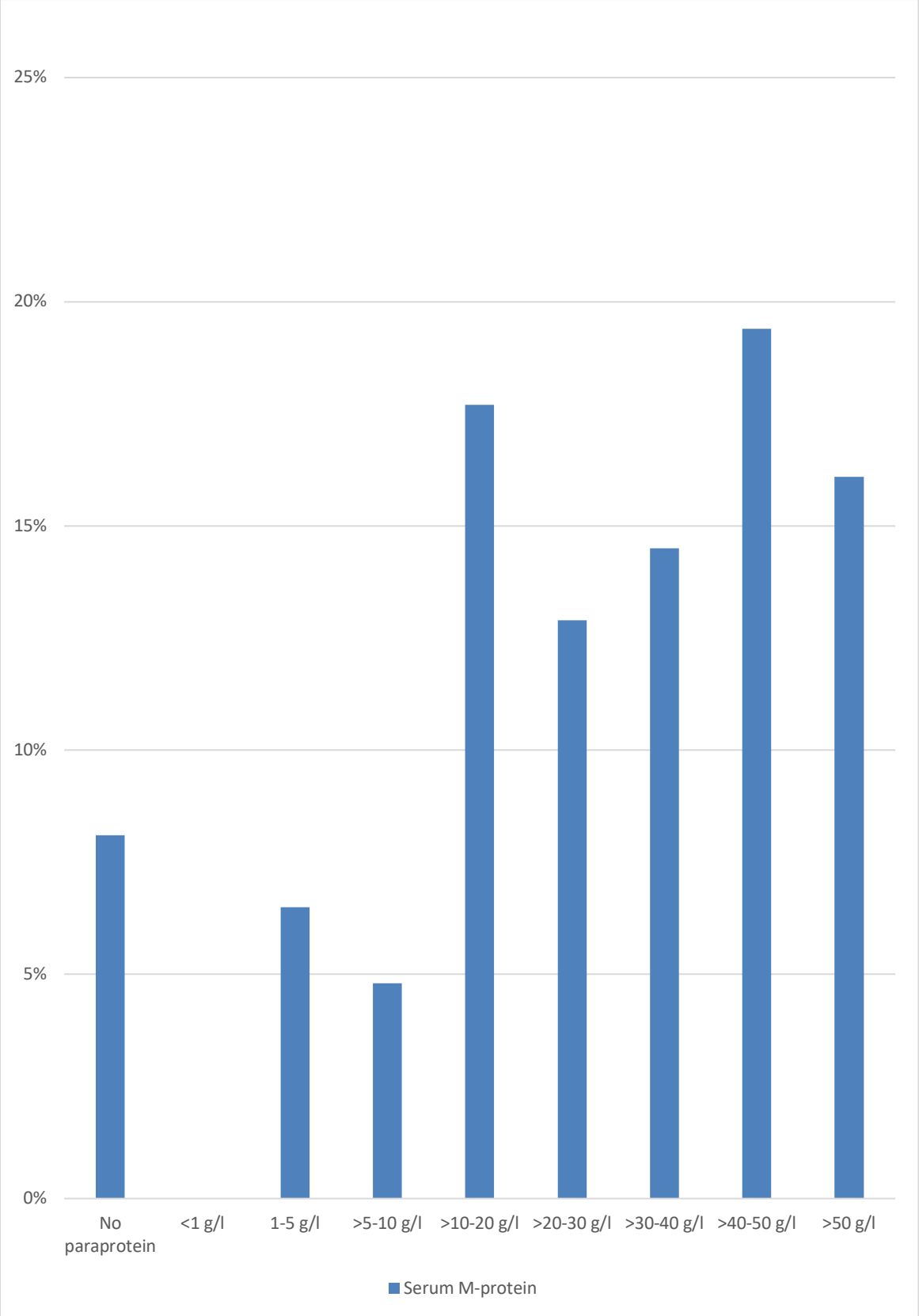


Figure 3.2: Serum M-protein levels in patients with Multiple Myeloma.

3.4. BONE MARROW FINDINGS

3.4.1. Bone Marrow Plasmacytosis

Bone Marrow Aspirate and Trephine results were available for 60 patients (85.7%). The percentage plasmacytosis is shown in Table 3.11. Of note,18% of the patients had a plasmacytosis of <10%, while 23% had a plasmacytosis of between 10 and 20%. A plasmacytosis above 30% was documented in 49% of the patients. Furthermore, 20% had a marked plasmacytosis of >60%.

Table 3.11: Percentage plasma cells in the Bone Marrow of patients with Multiple Myeloma

% Plasma cells	**Number**	**Percentage**
Mean (range)	35 (0-95)	
<10	11 (60)	18%
10 to 20	14 (60)	23%
>20 to 30	6 (60)	10%
>30 to 40	9 (60)	15%
>40 to 50	4 (60)	7%
>50 to 60	4 (60)	7%
>60	12 (60)	20%

3.4.2. Cytogenetic tests

One of the limitations of this retrospective study is the low percentage of cytogenetic results that are available for review. As all the BMAT biopsies were not necessarily performed by the staff of the Clinical Haematology Unit, cytogenetics may have been omitted in a number of patients, particularly where the diagnosis of MM may not have been suspected, at the time of doing the BMAT. Additional reasons could be the inability to obtain an adequate specimen for cytogenetics, specimens not reaching the cytogenetic laboratory timeously and failure to obtain an adequate number of metaphases on the submitted specimens for cytogenetic analysis. The cytogenetic results in the 20/60 patients (33%) are shown in Table 3.12 below.

Table 3.12: Cytogenetic results in patients Multiple Myeloma

Karyotype/cytogenetic abnormality	Number	Percentage
Normal female with no structural aberrations	9 (20)	45%
Normal male with no structural aberrations	6 (20)	30%
Partial/complete trisomy of chromosome 14 and 17	1 (20)	5%
Monosomy chromosome 17 with loss of TP53 gene	1 (20)	5%
Suboptimal/poor hybridization of the FISH probe	2 (20)	10%
BCR/ABL fusion gene	1 (20)	5%
Negative for t(11;14)	1 (20)	5%
Negative for TP53 deletion	11 (20)	55%
Negative for 13q14.3 deletion	14 (20)	70%
Negative for t(4;14)	16 (20)	80%
Negative for t(14;16)	2 (20)	10%
Negative for gain of 1q21.2	5 (20)	25%
Negative for 1p32.3 deletion	4 (20)	20%

3.5. RADIOLOGICAL FINDINGS

Of note, 60 of the patients (60/70 –86%) had some form of radiological investigation, including a skeletal survey, computerized tomographic scan (CT scan) or magnetic resonance imaging (MRI) scan.

3.5.1. Skeletal survey

Plain X-ray skeletal survey results were available for 48 patients (68.57%). Lytic lesions were found in 35 patients (73%), suspected plasmacytomas in 14 patients (29%), vertebral body compression fractures in 12 patients (25%) and pathological fractures of the long bones in 6 patients (12.5%). This is depicted in Table 3.13 below.

Table 3.13: Skeletal radiological findings in patients with Multiple Myeloma

Radiographic findings	Number	Percentage
Lytic lesions	35 (48)	73%
Suspected plasmacytoma	14 (48)	29%
Vertebral body compression fractures	12 (48)	25%
Pathological fractures of the long bones	6 (48)	12.5%

3.5.2. Computerized tomographic scan (CT scan) findings

Of note, 26 patients had CT scan results available for review (37%). The sites of the CT scan included the following: i) Thorax and spine (21 patients - 81%); ii) Abdomen and pelvis (13 patients - 50%), and iii) Head and neck (10 patients - 39%). Furthermore, the findings on CT

scan are summarized in Table 3.14 below, and include: a) Lytic lesions (20 patients – 77%), suspected plasmacytomas (19 patients – 73%) and vertebral body compression fractures (4 patients – 15%).

Table 3.14: Computerized tomographic scan (CT scan) findings in patients with Multiple Myeloma

Computerized tomographic scan (CT scan) findings	**Number**	**Percentage**
Lytic lesions	20 (26)	77%
Suspected plasmacytoma	19 (26)	73%
Vertebral body compression fractures	4 (26)	15%

3.5.3. Magnetic resonance image (MRI) findings

Of note, 31 patients had MRI scan results available for review (44%). The sites of the MRI scan included the following: i) Thorax and spine (30 patients –97%), and ii) Head and neck (6 patients - 19%). Furthermore, the findings on MRI scan are summarized in Table 3.15 below, and include: a) Vertebral body compression fractures (24 patients – 77%), b) Vertebral bone marrow signal intensity changes (19 patients – 61%), c) Spinal cord compression (14 patients – 45%), d) suspected plasmacytoma (12 patients – 39%) and d) lytic lesions (6 patients – 19%).

Table 3.15: Magnetic resonance imaging (MRI) findings in patients with Multiple Myeloma

Magnetic resonance image findings	**Number**	**Percentage**
Vertebral body compression fractures	24 (31)	77%
Vertebral bone marrow signal intensity changes	19 (31)	61%
Spinal cord compression	14 (31)	45%
Suspected plasmacytoma	12 (31)	39%
Lytic lesions	6 (31)	19%

On MRI scan of the spine, 14/31 (45%) of the patients had evidence of spinal cord compression. Further breakdown of the likely cause of spinal cord compression revealed the following: i) 7/14 (50%) had bony compression (vertebral body collapse with impingement of the spinal cord), and ii) in the remaining 7/14 (50%), the spinal cord compression was due to a soft tissue plasmacytoma. This is shown in Table 3.16 below.

Table 3.16: Causes of spinal cord compression in patients with Multiple Myeloma

Spinal cord compression	Number	Percentage
Compression from bone	7 (14)	50%
Compression from soft tissue plasmacytoma	7 (14)	50%

Regarding a detailed analysis of plasmacytomas, 20/68 (29%) had a clinically suspected plasmacytoma, 31/60 (52%) had radiological evidence of a plasmacytoma, 17/60 (28%) had both clinical and radiological evidence of a plasmacytoma and 15/60 (25%) had biopsy proven documentation of a plasmacytoma. This is shown in Table 3.17 below. Furthermore, of the 31 patients suspected of having a plasmacytoma radiologically, 13 (42%) had a solitary extramedullary plasmacytoma and 18 (58%) had an extramedullary plasmacytoma, together with evidence of systemic MM.

Table 3.17: Detailed analysis of plasmacytomas in patients with Multiple Myeloma

Plasmacytoma	Number	Percentage
Radiologically	31 (60)	52%
Clinically	20 (68)	29%
Clinically & radiologically	17 (60)	28%
Biopsy proven	15 (60)	25%

3.6. STAGING

Both the Salmon-Durie Stage as well as the International Staging System (ISS) were used to stage patients in this study.

3.6.1. Salmon-Durie Stage

Staging was calculated for 70 patients. Of the 70 patients, 5 patients (7.1%) had stage 1A disease, no patient had stage 1B disease, 1 patient (1.4%) had stage 2A disease, no patients had stage 2B disease, and the majority of the patients had stage 3 disease. Furthermore, 41 patients (58.6%) had stage 3A disease and 23 patients (32.9%) had stage 3B disease, respectively. This is depicted in Table 3.18 and Figure 3.3 below.

Table 3.18: Salmon-Durie Stage in patients with Multiple Myeloma

Salmon-Durie Stage	Number of patients	Percentage
Stage 1A	5 (70)	7.1 (7%)
Stage 1B	0 (70)	0%
Stage 2A	1 (70)	1.4% (1%)
Stage 2B	0 (70)	0 %
Stage 3A	41 (70)	58.6 (59%)
Stage 3B	23 (70)	32.9 (33%)

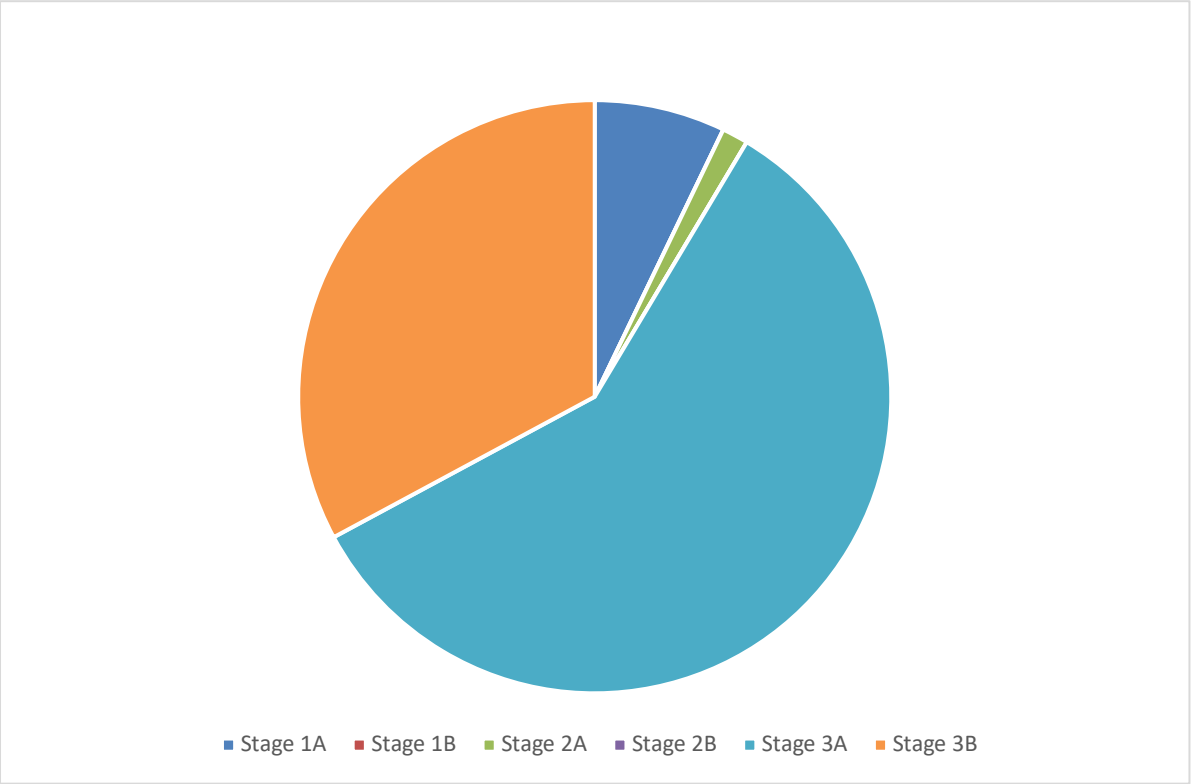


Figure 3.3: Salmon -Durie stage in patients with Multiple Myeloma

3.6.2. International Staging System

Staging was calculated for 54 patients based on parameters used in the ISS, i.e., the albumin level and the Beta 2 microglobulin (B2M) level. Stage 1 is characterized by a B2M level <3.5 mg/L and albumin <35 g/l. In stage 2, the B2M level is 3.5-5.5 mg/L together with any albumin level, or a B2M <3.5 mg/L and albumin <35 g/l, while in stage 3, the B2M level is ≥5.5 mg/L, with any albumin level. In the study, 6 patients (11%) had stage 1 disease, 10 patients (19%)

had stage 2 disease, and the majority had stage 3 disease, i.e. (70%). This is indicated in Table 3.19 and Figure 3.4 below.

Table 3.19: International Staging System in patients with Multiple Myeloma

International staging system	Number of patients	Percentage
Stage 1	6 (54)	11 %
Stage 2	10 (54)	19 %
Stage 3	38 (54)	70 %

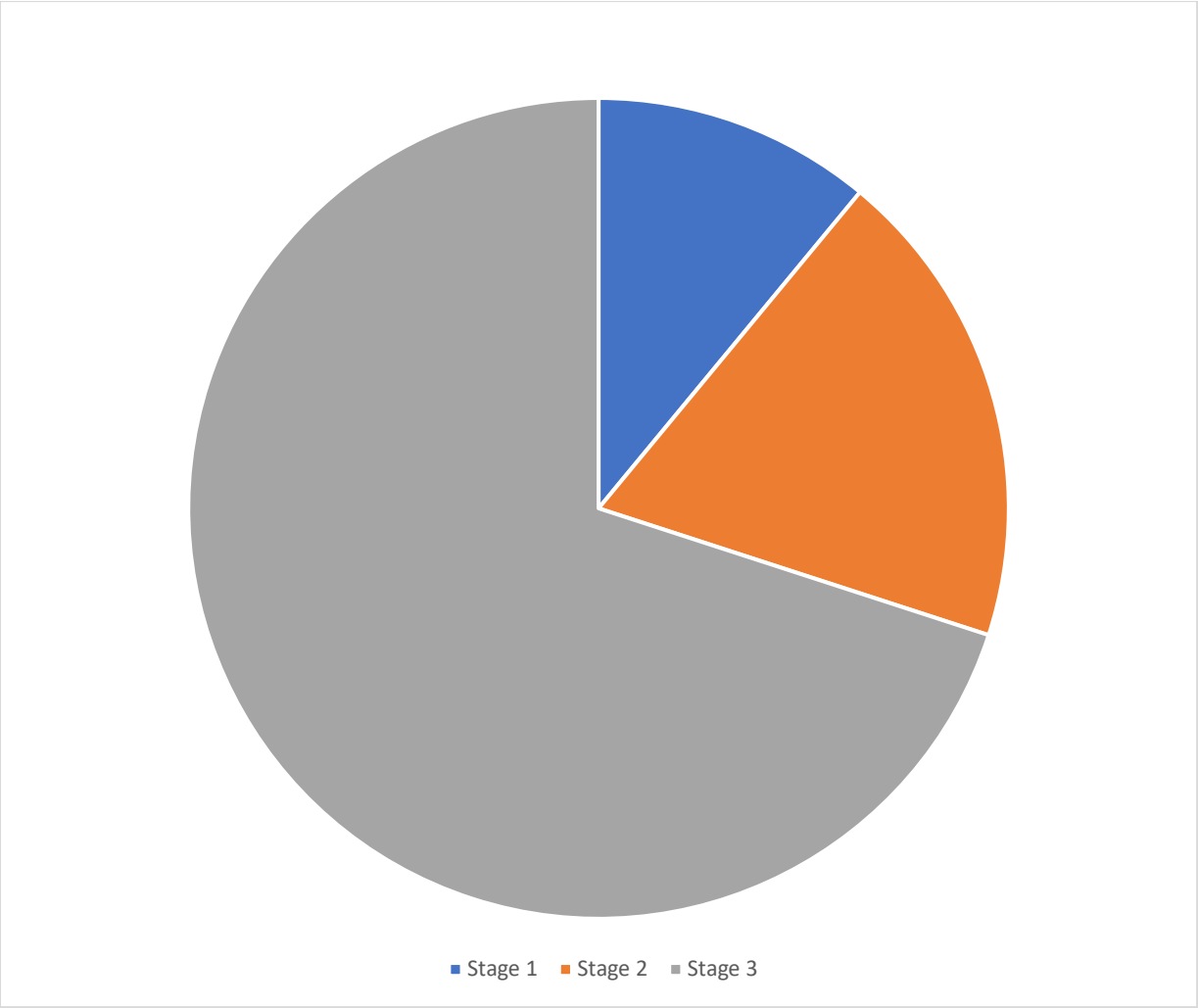


Figure 3.4: International Staging System in patients with Multiple Myeloma

3.7. THERAPY

3.7.1. Combination Antiretroviral Therapy

A total of 49/68 known HIV-1 sero-positive patients (72%), were on combination antiretroviral therapy (cART) at the time of the diagnosis of MM. Furthermore, 4 patients (known with HIV-

1 sero-positivity) (6%), were not on cART treatment, while 15 patients (22%), had newly diagnosed HIV-1, at the time of the MM diagnosis. This is shown in Table 3.20 below.
Of the 19 patients (28%), who were not on cART, 4 patients (21%) died prior to initiation of therapy, and in 15 patients (79%), cART was initiated by the Clinical Haematology Unit or the HIV Clinic at CHBAH.

Table 3.20: Combination Antiretroviral Therapy in patients with Multiple Myeloma

Combination antiretroviral therapy	**Number**	**Percentage**
Known patients with HIV-1 sero-positivity, on cARTat the time of MM diagnosis	49 (68)	72%
Known patients with HIV-1 sero-positivity, not on cART at the time of MM diagnosis	4 (68)	6%
Newly diagnosed HIV-1 sero-positivity, at the time of MM diagnosis	15 (68)	22%

3.7.2. Chemotherapy, radiotherapy and supportive care

Chemotherapy was administered to 53/70 (76%) patients. Of the 53 patients who received chemotherapy, 39/53 patients (74%) received CVAD (cyclophosphamide, vincristine, adriamycin, dexamethasone), 9/53 received melphalan and dexamethasone (17%), 3/53 received thalidomide and dexamethasone (6%), and 2/53 (4%) received CTD (cyclophosphamide, thalidomide, dexamethasone), as first line induction chemotherapy. This is indicated in Table 3.21 below.
Furthermore, 3/53 patients (6%) had an ASCT (autologous stem cell transplant) as part of consolidation, and 5/53 (9%) received maintenance chemotherapy.
External beam radiation therapy was administered in 18/53 patients (34%). Of the patients who received radiotherapy, 6/18 (33%) were for spinal cord compression and 12/18 (67%) for a plasmacytoma.
Lastly, 15/70 patients (21%) received supportive treatment only (i.e.no chemotherapy or radiotherapy), as shown below in Table 3.21 below.

Table 3.21: Therapy in patients with Multiple Myeloma

1st line induction regimen	**Number**	**Percentage**
CVAD (cyclophosphamide, vincristine, adriamycin, dexamethasone)	39 (53)	74%
Melphalan and dexamethasone	9 (53)	17%
Thalidomide and dexamethasone	3 (53)	6%
CTD (cyclophosphamide, thalidomide, dexamethasone	2 (53)	4%
Consolidation		
ASCT (autologous stem cell transplantation)	3 (53)	6%
Maintenance		
Thalidomide	5 (53)	9%
External beam radiation		
External beam radiation	18 (53)	34%
Supportive care		
Supportive care only (no chemotherapy or radiotherapy)	15 (70)	21%

3.7.3. Response to chemotherapy

The type of response to initial chemotherapy is shown in Table 3.22 below. A CR (complete response), VGPR (very good partial response) and PR (partial response) was noted in 4/53 (7.5%), 3/53 (5.7%) and 9/53 (16.9%) of the patients, respectively, while 11/53 (20.8%) and 4/53 (7.5) of the patients had SD (stable disease) or PD (progressive disease), respectively. Furthermore, 11/53 (20.8%) patients were lost to follow up, 8/53 (15.1%) died prior to completion of therapy and in 3/53 (5.7%) of the patients, there was inadequate information in the file regarding treatment response.

Table 3.22: Response to initial chemotherapy in patients with Multiple Myeloma

Depth of response	**Number**	**Percentage**
Complete response CR	4 (53)	7.5%
Very good partial response VGPR	3 (53)	5.7%
Partial response PR	9 (53)	16.9%
Stable disease SD	11 (53)	20.8%
Progressive disease PD	4 (53)	7.5%
Lost to follow-up	11 (53)	20.8%
Died before completion of chemotherapy	8 (53)	15.1%
Inadequate information available	3 (53)	5.7%

3.7.4. Best response to treatment

The best response to treatment is shown in Table 3.23 below. A slightly higher proportion of patients achieved a CR, VGPR and PR, compared to the initial response, as shown in Table 3.22 above.

Table 3.23: Best response to chemotherapy in patients with Multiple Myeloma

Depth of response	Number	Percentage
Complete response CR	5 (53)	9.4%
Very good partial response VGPR	6 (53)	11.3%
Partial response PR	11 (53)	20.8%
Stable disease SD	6 (53)	11.3%
Progressive disease PD	3 (53)	5.7%
Lost to follow-up	11 (53)	20.8%
Died before completion of chemotherapy	8 (53)	15.1%
Inadequate information available	3 (53)	5.7%

3.7.5. Response to treatment at last visit

The response to treatment at the last visit, in patients who had some form of documented response, as indicated in Tables 3.22 and 3.23 above, is shown in Table 3.24 below.

Table 3.24: Response at last visit in patients with Multiple Myeloma

Depth of response	Previously	Last visit
Complete response CR	5	3
Very good partial response VGPR	6	3
Partial response PR	11	3
Stable disease SD	6	3
Progressive disease PD	3	10

3.8. OUTCOMES AND SURVIVAL

3.8.1. Outcome

As of July 2023, only 3 patients (4.3%) in this cohort were still alive, 42 patients (60%) died and 25 (35.7%), were lost to follow-up. This is shown in Table 3.25 below.

Table 3.25: Outcome in patients with Multiple Myeloma

Outcome	Number	Percentage
Alive	3 (70)	4.3%
Dead	42 (70)	60%
Lost to follow-up	25 (70)	35.7%

3.8.2. Survival

Only 45 patients had survival data available for review. 18/45 (40%) had a survival of ≤ 3months, 12/45 (27%) a survival of >3 months to < 12 months, and 15/45 (33%) ≥ 12 months, as shown in Table 3.26 below.

Table 3.26: Survival in patients with Multiple Myeloma

Survival	**Number**	**Percentage**
Survival ≤ 3 months	18 (45)	40%
Survival >3 to <12 months	12 (45)	27%
Survival ≥12 months	15 (45)	33%

Table 3.27: Survival in patients who received chemotherapy and/or radiotherapy versus supportive treatment

	Chemotherapy and/or radiotherapy	Supportive therapy
Survival ≤ 3 months	7	11
Survival >3 to <12 months	12	0
Survival ≥12 months	23	0

Table 3.28: Survival in patients achieving a PR (Partial Response) versus less than PR on Chemotherapy

Response to Chemotherapy	≥ PR or better	<PR
Survival ≤ 3 months	0	0
Survival >3 to <12 months	2	4
Survival ≥12 months	18	2

Table 3.29: Survival based on the Durie-Salmon stage in patients with Multiple Myeloma

Durie-Salmon Stage	1A	1B	2A	2B	3A	3B
Survival ≤ 3 months	0	0	0	0	11	7
Survival >3 to <12 months	1	0	0	0	4	7
Survival ≥12 months	1	0	0	0	19	3

Table 3.30: Survival based on the International Staging System (ISS) in patients with Multiple Myeloma

ISS Stage	Stage 1	Stage 2	Stage 3
Survival ≤ 3 months	0	1	14
Survival >3 to <12 months	1	1	9
Survival ≥12 months	4	5	10

Table 3.31: Survival related to the initial CD4 count

CD4 Count	CD4 ≥200 cells/ul	CD4 >100 -<200 cells/ul	CD4<100 cells/ul
Survival ≤ 3 months	11	3	3
Survival >3 to <12 months	7	4	1
Survival ≥12 months	16	0	4

Kaplan-Meier (KM) survival curves for the HIV-1 sero-positive patients are shown below.

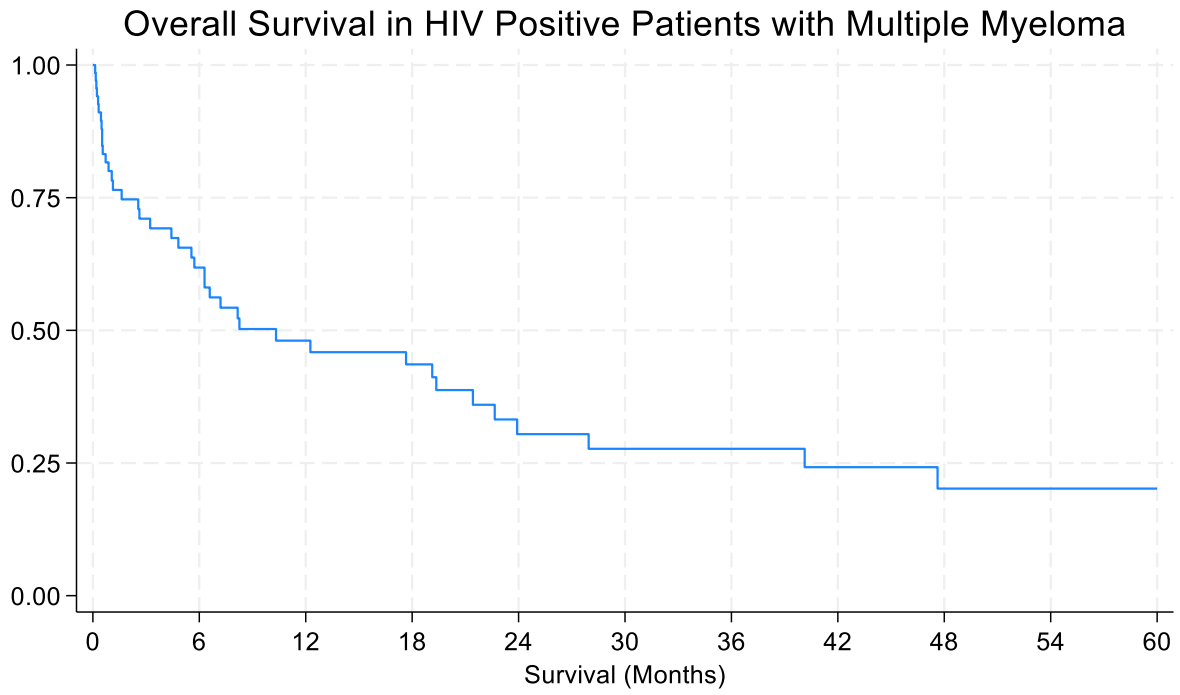


Figure 3.5: Overall survival in HIV-1 sero-positive patients with Multiple Myeloma

The median overall survival was 5.64 months (Interquartile range 0.82 – 19.24).

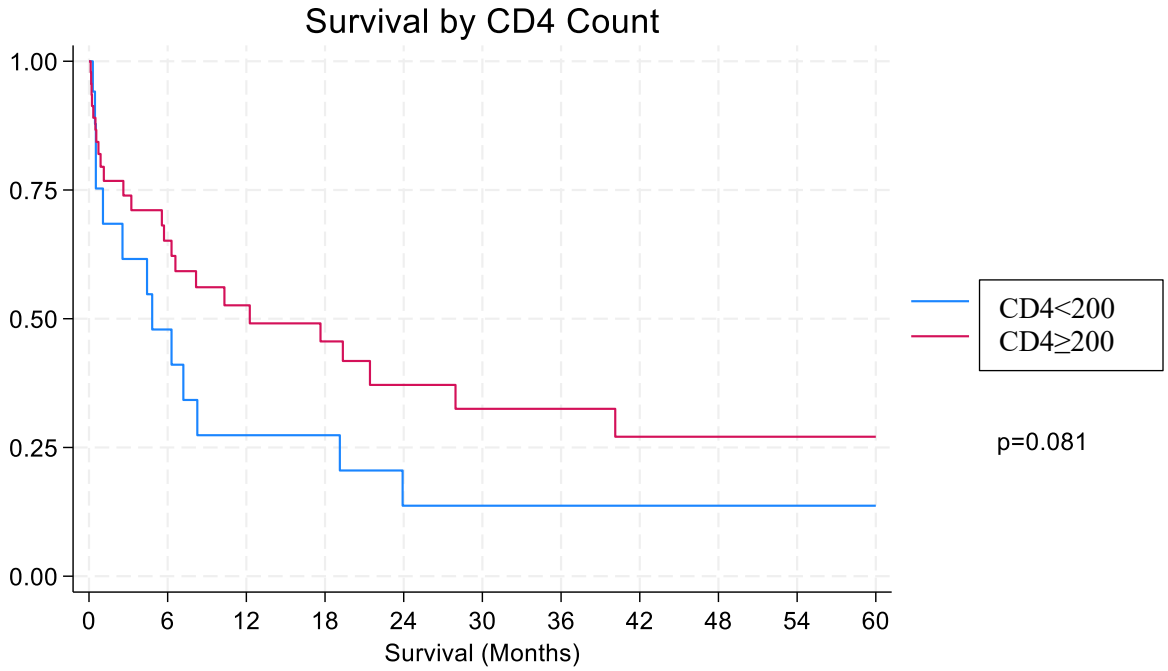


Figure 3.6: Survival by CD4 Count in HIV-1 sero-positive patients with Multiple Myeloma

Patients with CD4 counts ≥ 200 cells/ul had better survival than patients with CD4 counts<200 cells/ul, although this difference did not reach statistical significance (p=0.081).

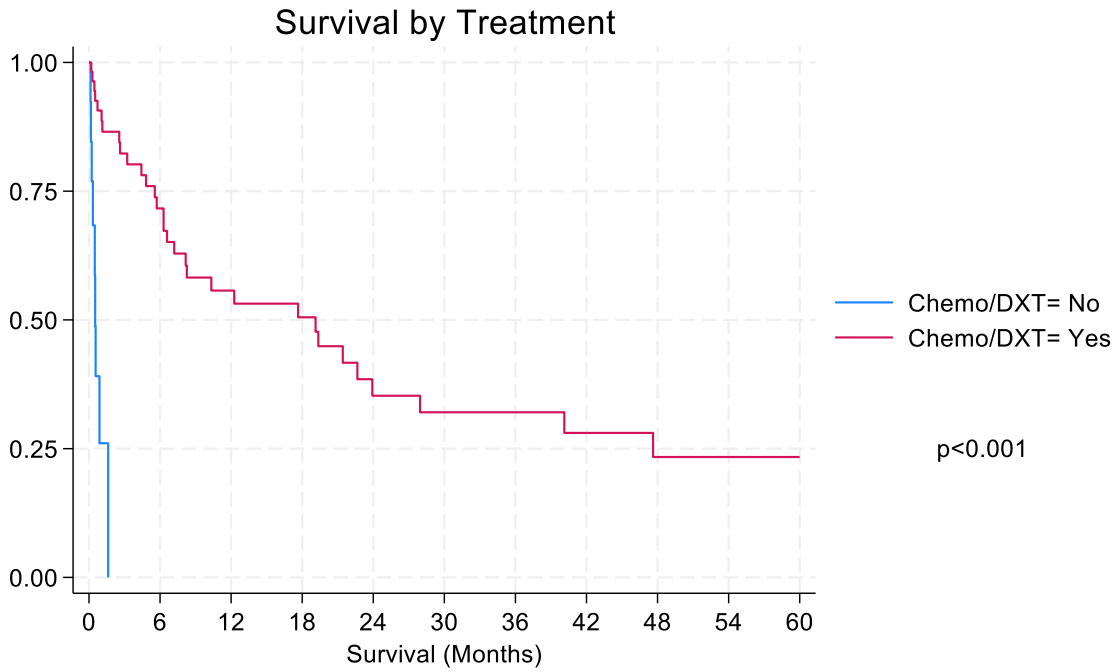


Figure 3.7: Survival by definitive treatment (chemotherapy and radiotherapy) versus supportive therapy in patients with HIV-1 sero-positive Multiple Myeloma

There were marked differences in patients who received definitive treatment (i.e. chemotherapy and/or radiotherapy) compared to those who did not. These differences were statistically significant, p<0.001.

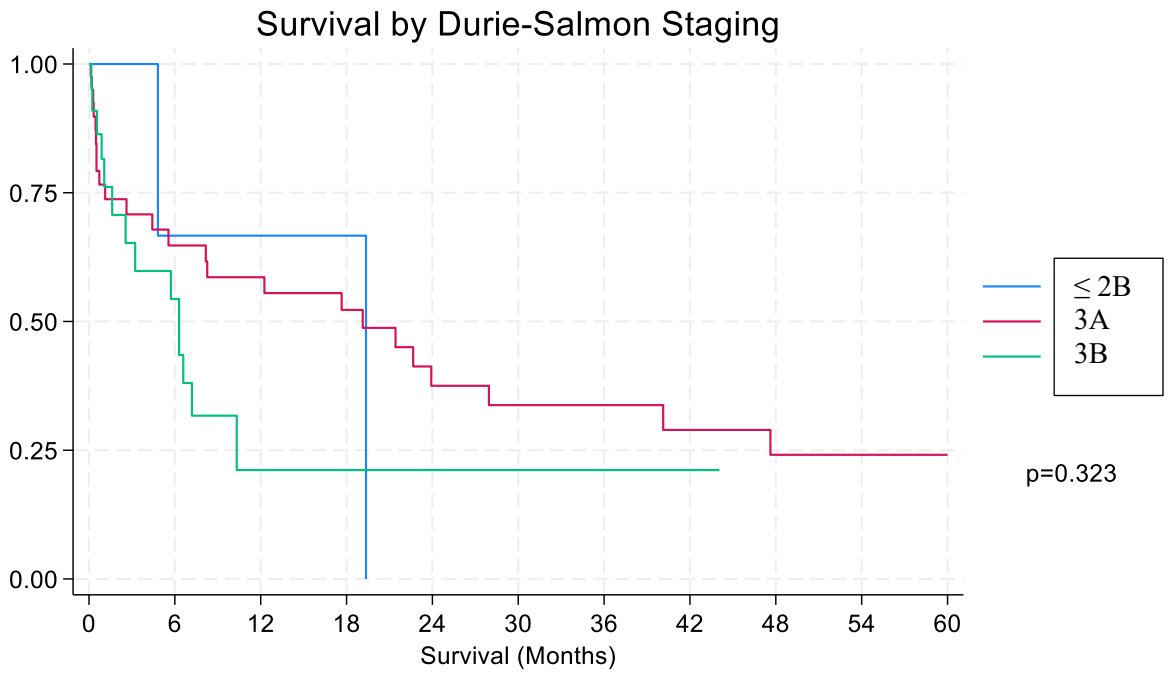


Figure 3.8: Survival by Durie-Salmon (DS) staging in HIV-1 sero-positive patients with Multiple Myeloma

Differences in survival by DS staging were not statistically significant, p=0.323.

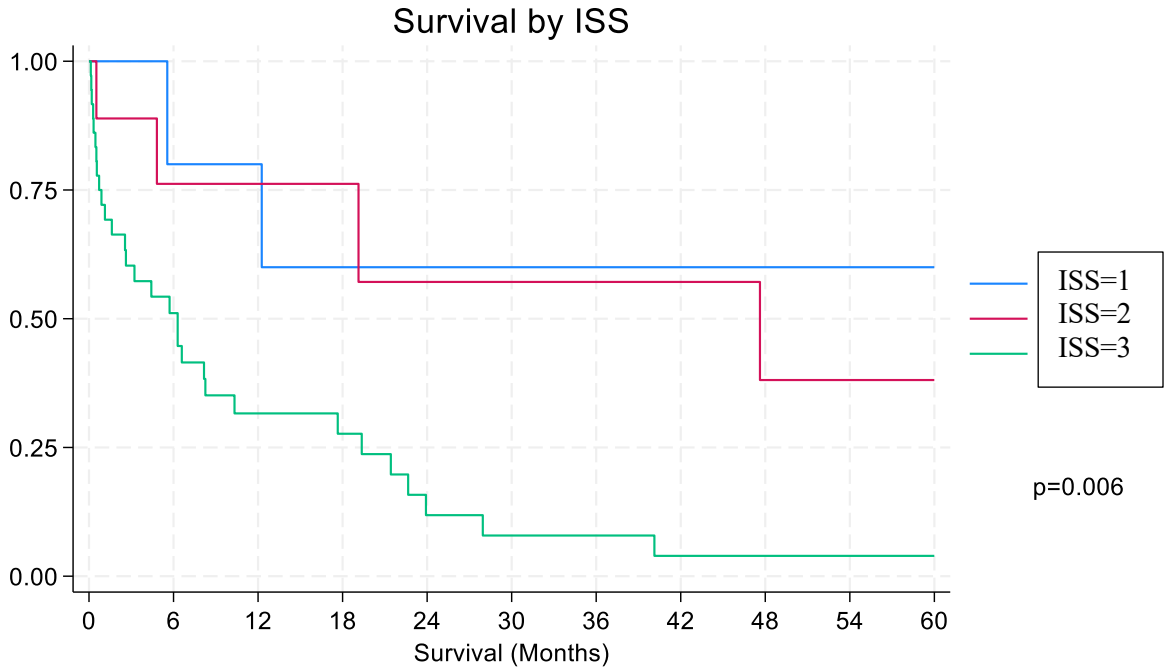


Figure 3.9: Survival by International Staging System (ISS) in HIV-1 sero-positive patients with Multiple Myeloma

Patients with ISS 1 and 2 had much better survival than those with ISS 3 and these differences were statistically significant, p=0.006.

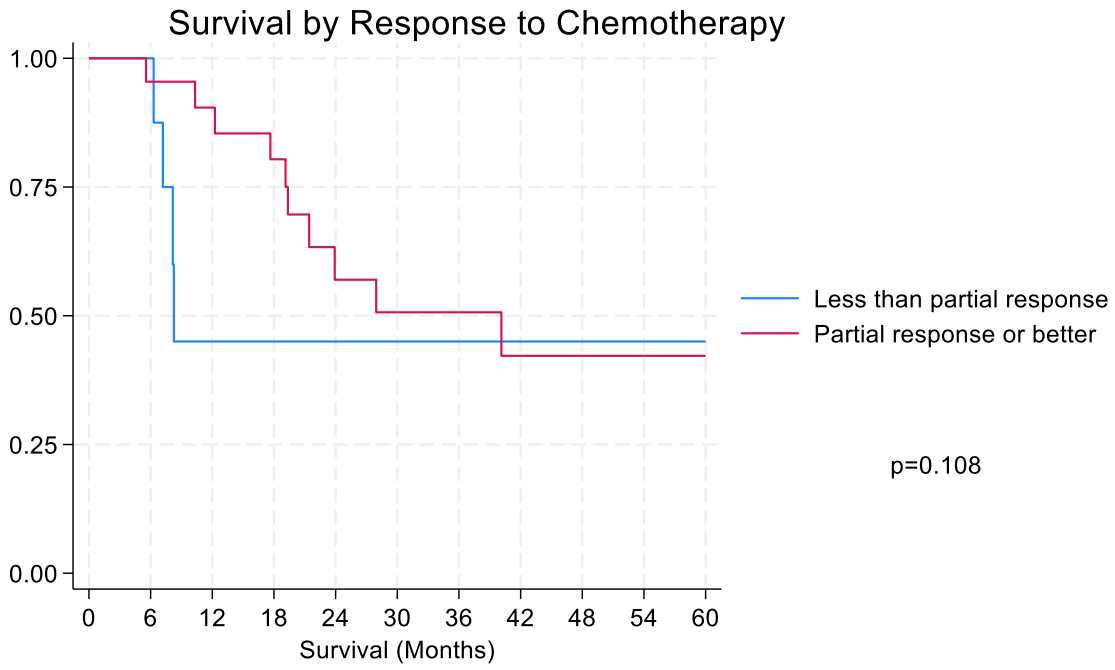


Figure 3.10: Survival by response to chemotherapy (PR versus <PR) in HIV-1 sero-positive patients with Multiple Myeloma

Patients with at least a partial response to chemotherapy or better had superior survival than those who did not, although this difference did not reach statistical significance (p=0.108).

4.0. CHAPTER 4: DISCUSSION

Multiple Myeloma (MM) is a haematological malignancy characterized by the proliferation of plasma cells in the bone marrow (1). The dominant clinical features of this malignant plasma cell proliferation and its resultant immunoglobulin secretion (including both heavy and light chain isotypes) include i) Skeletal manifestations (such as bone pain, lytic bone lesions, pathological fractures of the long bones, vertebral body compression fractures, osteopenia/osteoporosis, hypercalcaemia and spinal cord compression), ii) Anaemia, iii) Renal dysfunction and iv) An increased susceptibility to infection (7).

4.1. EPIDEMIOLOGY AND DEMOGRAPHIC FEATURES

The incidence of MM varies substantially across the different continents, with the highest rates reported in North America and some parts of Europe, intermediate rates in other parts of Europe and Africa, and the lowest rates in Asia. MM occurs more commonly in people of Afro-Caribbean descent, with the incidence being two-fold higher in African Americans compared to Caucasians (1,4,5). In South Africa, prior to the advent of and impact of HIV, MM was the most common haematological malignancy in adults (7,8). However, since 2002, Non-Hodgkin Lymphoma (NHL) has superseded MM, with MM being the second most common haematological malignancy encountered in adults, currently (8).

At Chris Hani Baragwanath Academic Hospital (CHBAH), MM has been a stable disease (with respect to patient numbers), since the 1970's (7,9,12). During the study period (01/01/2006 to 31/12/2020 – 15 years), a total of 601 patients were newly diagnosed with MM (average of 40 patients per year). 84 patients were HIV-1 sero-positive (14%). Of these 84 patients, 14 were excluded (see chapter 2.0 for details). Thus, a total of 70 evaluable HIV-1 sero-positive patients were included in this study (12%). In the first five years of the current study (2006-2010), the total number of patients seen at CHBAH with MM was 165 (average of 33 new patients per year). In the second five years of the study (2011-2015), the total number was 168 (average of 34 new patients per year). However, in the latter five years of the study (2016-2020), the number increased substantially to 268, with an average of 54 new patients seen per year. Similarly, the impact of HIV-1 sero-positivity has been stable for the first five years and second five years of the study (18/165 – 10.9%, and 17/168 – 10.1%), respectively. However, in the latter five years of the study, there has been a notable increase in HIV-1 sero-positivity by 2.8-fold in the period 2016-2020, with the total number of HIV-1 sero-positive individuals increasing to 49, from 18 and 17, respectively (49/219 – 18.3%) (see Figure 3.1 and Table 3.1). This is in keeping with the increasing

background HIV seroprevalence noted for Gauteng over the same period (60).

MM is characteristically a disease of middle-aged and elderly individuals. In the Western world, ninety-eight percent of cases occur over the age of 40 years with a peak in incidence in the seventh decade. The median age at diagnosis is 66 years (1,11). However, in Africa, the disease presents at a younger median age (approximately 5-10 years younger), with 7% of the patients being under the age of 40 years, based on a local study by Patel, 2000 (7). Furthermore, in his review of 170 patients with MM, studied between 1992 and 1997, the mean age at diagnosis was 61 years, and the male to female ratio was 1.45:1 (7). In 2016, van der Walt, in an extension to the above study at Chris Hani Baragwanath Academic Hospital (CHBAH), showed a median age at diagnosis of 58 years, with a male to female ratio of 1:1, in his review of 289 patients with MM, between 1998 and 2010. The peak age frequency (36.2% and 28.6%) in his study, was in the 6^{th} and7^{th} decades, respectively (12). Of the 70 evaluable HIV-1 sero-positive patients included in this study, there were 42 females and 28 males with a female to male ratio of 1.5:1. The mean age for females was 49.9 years (range 31-77 years), and males was 50.6 years (range 36-73 years), while the mean age for the whole group was 50.2 years (range 31-77years). This younger age is in keeping with both the younger age of MM diagnosis in Africa, and the younger age at diagnosis of HIV-1 sero-positive MM, as shown in the literature (7,12,94,95,97,102-121). What is different in this study, is the female predominance of 1.5:1 in HIV-1 sero-positive MM, as compared to studies done in the Western World, where there is a male predominance (94,107,108). The reason for this difference is the HIV-1 sero-positive 'risk group', being predominantly homosexual males and illicit intravenous drug users in the Western World, as compared to heterosexual females and males, in the local context (94,107,108).

4.2. CLINICAL FEATURES AND LABORATORY FINDINGS

As indicated previously, our patients with MM are usually symptomatic and tend to present late, at an advanced stage of disease, with overt clinical manifestations. The Eastern Co-operative Group (ECOG) performance status is an indication of the functional impact/status of the disease on our patients and is indicated in Table 3.3. As expected, more than half of the patients (54.7%) had a performance status (PS) of ≥ 2.

The most common clinical findings at presentation are shown in Table 3.2. Bone pain was the most frequently reported symptom (79%), and pallor, the most common physical sign (48%). However, laboratory evidence of anaemia was evident in 86% of the patients at presentation

(see Table 3.5).This is in keeping with local and other studies, where bone pain and anaemia are the most common symptoms/signs at presentation (Patel, 2000 – bone pain 94%, anaemia 81%); (van der Walt, 2016 – bone pain 87%, anaemia 92%); (Doualla-Bija, et al, 2014 –bone pain 76%, anaemia 71%) (7,12,110), including HIV-1 sero-positive MM (de Groot, et al, 2017 –Bone pain 100%); (Nanho et al, 2019 – bone pain 100%, anaemia 100%) (95,108).

Anaemia is the dominant cytopenia in MM. The mean haemoglobin (Hb) at presentation was 8.78 g/dl, with a range of 3-17.9 g/dl. It was characteristically normocytic (69%) and grade 3 and 4 anaemia was present in 29% and 18% of the patients, respectively (see Table 3.5). Compared to anaemia, leucopenia and thrombocytopenia are seen in the minority of patients with MM, at presentation. The mean white cell count (WCC) was 6.65, with a range of 1.56 to 18.8 x 10^9/l. Leucopenia and leucocytosis were evident in 12% and 7% of the patients, respectively. Neutropenia was present in 16.5%, with grade 3 and 4 being present in 1.5% and 3% of the patients, respectively (see Table 3.5). The mean platelet count was 230 x 10^9/l. Clinical thrombocytopenia was present in 13%, while thrombocytosis was evident in 6% of the patients at presentation (see Table 3.5). It is plausible that the co-existence of HIV-1 together with MM, contributes to the generally more severe cytopenias evident in this cohort of patients. Strangely, weight loss was documented in 77% of the patients (this is more likely attributable to the HIV, as it is an uncommon presenting feature of MM). Additionally, clinical evidence of plasmacytoma and neurological signs were noted in 29% and 28% of the patients, respectively, while radiologically evident plasmacytomas were noted in 52% of the patients (see Tables 3.2 and 3.17).

Table 3.6 shows the CD4 counts at presentation. The mean CD4 count was 367 cells/ul, with a range of 23-964 cells/ul. The CD4 count was <200cells/ul in 26.1% of the patients, while 76.9% had a CD4 count of <500cells/ul. A CD4 count of <50cells/ul was only seen in 4.6% of the study patients. A total of 49/68 known HIV-1 sero-positive patients (72%), were on combination antiretroviral therapy(cART) at the time of the diagnosis of MM. 4 patients (known with HIV-1 sero-positivity) (6%), were not on cART treatment, while 15 patients (22%), had newly diagnosed HIV-1, at the time of the MM diagnosis. Of the 19 patients (28%), who were not on cART, 4 patients (21%) died prior to initiation of therapy, and in 15 patients (79%), cART was initiated by the Clinical Haematology Unit or the HIV Clinic at CHBAH (see Table 3.20). The CD4 count is an indirect measure of the stage of HIV, with lower CD4 counts generally implying a more advanced stage of disease, with a higher propensity to infective complications (opportunistic infections), such as Tuberculosis (TB).

With regard to the association of TB in this study cohort, 19% had a past history of TB, 1% had a simultaneous new diagnosis of TB, at the time of the diagnosis of MM, and 3% developed TB during the follow up course of their disease. This is depicted in Table 3.4.

Table 3.7 shows the biochemistry results in the study patients. Interestingly, the mean vitamin B12 level was 538 pmol/l, with a range of 106 to 1881 pmol/l. No patients had low vitamin B12 levels. This finding is unusual as there is a documented association of MM with vitamin B12 deficiency, ranging from 4.3% to 13.6% (125,126). The absence of vitamin B12 deficiency in our study may partly be a reflection of the younger patient population, and therefore less concomitant vitamin B12 deficiency.

The mean LDH was 487 U/L, with a range of 100 to 4079 U/L. The LDH level was elevated in 86% of the patients and likely reflects the more advanced nature of our patient presentation.

The mean uric acid level was 0.42 mmol/l, with a range of 0.08 to 0.99 mmol/l. The uric acid was elevated in 29% of females and 18% of males, respectively. This is consistent with malignant nature of the disease and the renal impairment evident in a subset of patients.

The mean corrected calcium level was 2.8 mmol/l, with a range of 2.02 to 4.03 mmol/l. Hypocalcaemia was evident in only 2% of the patients, while hypercalcaemia was present in 56% of the patients, with a level of >2.75 mmol/l being present in 40% of the patients at presentation. The high percentage of patients with hypercalcaemia is in keeping with our previous MM studies and also in patients with HIV-1 sero-positive MM (Patel, 2000 - 39%); (van der Walt, 2016 – 35%); (Nanho, et al, 2019 – 60%); (El-Husseiny, et al, 2014 – 40%) (7, 12, 108,111).

Renal dysfunction is a common complication of MM. The mean urea level was 11.4 mmol/l, with a range of 1.6 to 42.7 mmol/l. An elevated urea level was found in 46% of the patients. With regard to the serum creatinine, the mean value was 296 umol/l, with a range of 40 to 1954 umol/l. 45% of the patients had an elevated creatinine level, with 33% of the patients having a creatinine level above 177umol/l. This is similarly high, as in other African studies (van der Walt, 2016 – 32%); (Kiraka, et al, 2014 – 52%); (Nanho, et al, 2019 – 30%) (12,108,112).

The mean total protein level was 94 g/l, with a range of 49 to 153 g/l. An elevated total protein was seen in 62% of the patients. On further analysis of the total protein levels, the globulin fraction was elevated in 72% of the patients. The mean globulin level was 63 g/l, with a range of 17 to 136 g/l. Conversely, the mean albumin level was 32 g/l, with a range of 13-47 g/l. Hypoalbuminaemia was present in 65% of the patients at presentation and in the absence of an overt cause of hypoalbuminaemia (such as increased urinary loss, liver synthetic dysfunction,

malabsorption etc.) is a biomarker of disease severity, as evidenced in the International Staging System (ISS) and the revised ISS (R-ISS) (47,48).

The mean Beta 2 microglobulin (B2M) level was 14.5 mg/L, with a range of 2.3 to 66.4 mg/L. The B2M was elevated in the vast majority of patients (96.3%), with levels ≥3.5 mg/L in 81.5% and >5.5 mg/L in 70.4%, respectively. This is a reflection of the significant disease burden in our patients and contributed to by the concomitant renal dysfunction.

A M-protein (paraprotein) was present in 92% of the patients, as indicated in Table 3.8. In approximately half of the patients (48.5%), the paraprotein level was >30 g/l. Table 3.9 shows the serum free light chain results. Kappa light chains were detected in 73% of the patients (with 62.1% being clonal), while lambda light chains were evident in 55% (with 32.8% being clonal) (see also Table 3.10). The non-clonal contribution to the serum free light chains was most likely contributed to from the HIV-1 sero-positivity. An abnormal serum free light chain ratio was present in 49% of the study population.

Table 3.10 shows the different MM isotypes found in this study. IgG MM was the most common (74.2%), with 46.6% of the patients having an IgG kappa and 27.6% having an IgG lambda isotype, respectively. IgA MM was the second most common (17.3%), with IgA kappa being present in 12.1% and IgA lambda in 5.2%, respectively. Light chain only MM accounted for 3.4%, while non-secretory MM was also present in 3.4% of the patients in this study. While the most common isotype in this study (IgG), is in keeping with prior local studies (7,12), the higher percentage in this study is in keeping with other higher HIV-1 sero-positive MM studies, where the dominant and in some instances the only isotype is IgG (95,102,107,109).

4.3. BONE MARROW AND CYTOGENETIC ANALYSIS

Bone Marrow Aspirate and Trephine (BMAT) results were available for 60 patients (85.7%). The percentage plasmacytosis is shown in Table 3.11. 18% (11/60) of the patients had a plasmacytosis of <10% (4 out of the 11 patients had a biopsy proven plasmacytoma) and 23% had a plasmacytosis of between 10 and 20%. A plasmacytosis above 30% was documented in 49% of the patients. Furthermore, 20% had a marked plasmacytosis of >60%. Both HIV and MM may cause a plasmacytosis. However, with the help of flow cytometry, it is easy to confirm clonality of the plasma cells. This together with the trephine biopsy, which can be subjected to immuno-histochemistry allows one to differentiate clonal from reactive plasmacytosis. However, the diagnosis of MM was made using a combination of criteria (as indicated in the diagnostic criteria in chapter one) and the BMAT added value to the constellation of features required for a definitive diagnosis.

Although the BMAT can be used as a vehicle for cytogenetic testing (which is of prognostic significance), it was deemed to be one of the limitations of this retrospective study, as a very low percentage of cytogenetic results were available for review in this study. As all the BMAT biopsies were not necessarily performed by the staff of the Clinical Haematology Unit, cytogenetics may have been omitted in a number of patients, particularly where the diagnosis of MM may not have been initially suspected, at the time of doing the BMAT. Additional reasons could be the inability to obtain an adequate specimen for cytogenetics, specimens not reaching the cytogenetic laboratory timeously and failure to obtain an adequate number of metaphases on the submitted specimens for cytogenetic analysis. Issues related to adequate staffing at the cytogenetic laboratory to analyse the specimens may have posed a further challenge to the poor cytogenetic yield in this study. The cytogenetic results in 20/60 patients (33%), in whom it was performed is shown in Table 3.12. Unfortunately, no definitive conclusions could be made regarding the relatively non-specific nature of the results obtained on the small number of patients analysed.

4.4. RADIOLOGICAL FINDINGS

Radiological investigations included plain X-rays (such as the skeletal survey), computerized tomographic (CT) scans and magnetic resonance imaging (MRI) scans (see Tables 3.13 to 3.17). Overall, lytic bone lesions (the most common radiological finding in MM) were found in up to 73% to 77% of the patients (both on skeletal survey and CT, respectively). This concurs with the findings in other studies (Patel, 2000 – 88%); (van der Walt, 2016 – 90%); (de Groot, et al, 2017 – 73%); (Kiraka, et al, 2014 – 62%) (7,12,95,112). Surprisingly, there was a very high proportion of patients (77%) reported with vertebral compression fractures on MRI scanning (higher than the approximately 38-50%) reported in other studies (7,12,95,110,112), and suspected plasmacytomas (73%) on the select group of patients who had a CT scan. Pathological fractures of the long bones were noted in 12.5% of the patients.

On MRI scan of the spine, 14/31 (45%) of the patients had evidence of spinal cord compression. Further breakdown of the likely cause of spinal cord compression revealed the following: i) 7/14 (50%) had bony compression (vertebral body collapse with impingement of the spinal cord), and ii) in the remaining 7/14 (50%), the spinal cord compression was due to a soft tissue plasmacytoma (see Table 3.16).

With regard to a detailed analysis of plasmacytomas, 20/68 (29%) had a clinically suspected plasmacytoma, 31/60 (52%) had radiological evidence of a plasmacytoma (which includes the 19/26 (73%) who had evidence of this on the CT scan), 17/60 (28%) had both clinical and

radiological evidence of a plasmacytoma and 15/60 (25%) had biopsy proven documentation of a plasmacytoma. This is shown in Table 3.17. Furthermore, of the 31 patients suspected of having a plasmacytoma radiologically, 13 (42%) had a solitary extramedullary plasmacytoma and 18 (58%) had an extramedullary plasmacytoma, together with evidence of systemic MM. Plasmacytoma, as an extramedullary manifestation of MM, is more commonly reported in HIV-1 sero-positive MM (7,12,95,104,105,107). Therefore, the findings in this study are entirely in keeping with plasmacytoma being a more common and characteristic clinical and radiological manifestation of HIV-1 sero-positive MM.

4.5. STAGING

The results of the Durie-Salmon stage and the International Staging System (ISS) are shown in Tables 3.18 and 3.19 and Figures 3.3 and 3.4, respectively. As expected, and in keeping with the prior local studies, an advanced stage of disease was noted, utilizing both the Durie-Salmon stage (Stage 3A and 3B, accounting for 59% and 33% of the patients, respectively) and the ISS (Stage III, being present in 70% of the patients) (7,10,12).

4.6. THERAPY

The treatment of patients with MM is detailed in the literature review. It includes both supportive care and specific modalities of treatment. An important aspect of supportive care and a cornerstone of the therapeutic armamentarium for patients with MM, who are HIV-1 sero-positive, is combination anti-retroviral therapy (cART) and prophylaxis of opportunistic infections, particularly in patients where the CD4 counts are < 200 cells/ul. Where a patient was known to be HIV-1 sero-positive and on cART, the cART was continued and optimised. Where a patient was newly diagnosed, therapy was initiated as soon as possible. The use of cART in the patient cohort in this study is shown in Table 3.20.

Unfortunately, with regard to the availability of optimal specific therapy for MM, there are major limitations in our state sector / public sector hospitals. This is with particular reference to the novel agents, including the immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies, as part of the optimal and ‘state of the art’ therapy. While many of the patients were transplant eligible based on their age below 65 years, the late presentations and advanced stage of disease with its attendant co-morbidities (including HIV-1 sero-positivity - although HIV per se was not a contraindication to autologous stem cell transplantation (AutoSCT), had an impact on how patients with HIV-1 sero-positivity and MM were managed during the course of their disease.

Chemotherapy was administered to 53/70 (76%) patients. 39/53 patients (74%) received CVAD (cyclophosphamide, vincristine, adriamycin, dexamethasone), 9/53 received melphalan and dexamethasone (17%), 3/53 received thalidomide and dexamethasone (6%), and 2/53 (4%) received CTD (cyclophosphamide, thalidomide, dexamethasone), as first line induction chemotherapy. This is indicated in Table 3.21.

3/53 patients (6%) had an ASCT (autologous stem cell transplant) as part of consolidation, and 5/53 (9%) received maintenance chemotherapy (using 'lower doses' of thalidomide, typically 50mg to 100mg daily, in order to decrease the adverse effects of the drug, particularly with reference to peripheral neuropathy).

18/53 patients (34%) received external beam radiation therapy. Of the patients who received radiotherapy, 6/18 (33%) were for spinal cord compression and 12/18 (67%) for a plasmacytoma.

15/70 patients (21%) received supportive treatment only (i.e.no chemotherapy or radiotherapy), based on their poor clinical picture or attendant disease or HIV-1 related complications, as shown in Table 3.21.

The type of response to initial chemotherapy is shown in Table 3.22. A CR (complete response), VGPR (very good partial response) and PR (partial response) was noted in 4/53 (7.5%), 3/53 (5.7%) and 9/53 (16.9%) of the patients, respectively, while 11/53 (20.8%) and 4/53 (7.5%) of the patients had SD (stable disease) or PD (progressive disease), respectively. 11/53 (20.8%) were lost to follow up. 8/53 (15.1%) of the patients died prior to completion of therapy and in 3/53 (5.7%) of the patients, there was inadequate information in the file regarding treatment response.

A further attempt was made to assess the best response to therapy during the course of the patient's illness. A slightly higher proportion of patients achieved a CR, VGPR and PR, compared to the initial response, as shown in Table 3.22.

Finally, the response to treatment at the last visit was documented and is shown in Table 3.24. A sustained CR, VGPR and PR was sustained in 3/5, 3/6 and 3/11 patients, respectively. 3/6 patients continued to have stable disease, while 7/10 patients had progression of disease.

4.7. OUTCOMES AND SURVIVAL

Of the total cohort of 70 patients diagnosed between 01/01/2006 to 31/12/2020, the outcomes at the final review in July 2023 were as follows: 3 patients (4.3%) were still alive, 42 patients (60%) died and 25 (35.7%), were lost to follow-up. This is shown in Table 3.25.

45/70 (64%) of patients had survival data available for review. 18/45 (40%) had a survival of ≤ 3months, 12/45 (27%) a survival of >3 months to < 12 months, and 15/45 (33%) ≥ 12 months, as shown in Table 3.26. The median overall survival was 5.64 months (Interquartile range 0.82 – 19.24) (see KM survival curve, Figure 3.5). This is much lower, compared to two prior MM studies done at CHBAH (Patel, 2000 – median survival 15.5 months, 2/170=1.17% HIV-1 sero-positivity; van der Walt, 2016 – median survival 15.9 months, 18/289=6.2% HIV-1 sero-positivity) (7,12).

When assessing survival in relation to a number of parameters, the following was noted: i) Survival was better in patients with a higher CD4 count (≥200 cells/ul versus <200 cells/ul) at presentation, although this difference did not reach statistical significance (p=0.081) (see Figure 3.6), ii) Survival was statistically significantly better in patients who received chemotherapy and or radiotherapy versus supportive care only (p<0.001) (see Figure 3.7),iii) Survival by DS staging was not statistically significantly different (p=0.323) (see Figure 3.8). However, survival was statistically significantly different using the ISS stage (p=0.006) (see Figure 3.9) and iv) Survival was better in patients who achieved at least a PR to therapy as the best response, compared to those who achieved less than a PR, although this did not reach statistical significance (p=0.108) (see Figure 3.10).

In general, survival was inferior in our patients, compared to other studies of HIV-1 sero-positive MM patients in the literature, including the two local studies mentioned above, which had smaller numbers of HIV-1 sero-positive patients. Possible reasons for the poor survival include: i) delays in presentation to a tertiary healthcare centre, with subsequent delays in confirming a definitive diagnosis, ii) presentation with more advanced stage disease, iii) more acute complications which may impact on the timeous initiation of specific therapy, iv) 'sub-optimal' therapy as a result of the public sector health care challenges and v) the significant number of patients who are lost to follow up, as a result of socio-economic and other challenges. These limitations need to be addressed in further prospective studies in patients with MM, who by virtue of the malignant nature of the disease have significant morbidity and mortality related to the disease and its potential associations (such as HIV-1, particularly in our setting) and its varied complications.

4.8. LIMITATIONS OF THE STUDY

1. Retrospective nature of the study, hampered by incomplete and inadequate data in some of the patients,

2. Single centre study, with limited number of patients. However, paradoxically, when this

study is published, it will (to our current knowledge) be the largest study of HIV-1 sero-positivity in association with MM,

3. The high number of patients lost to follow up, primarily because of the poorer socio-economic status of the patients in this study,

4. Delays in presentation to hospital, diagnostic delays and delays in initiation of specific treatment (this is a global problem at tertiary, specialized, public healthcare facilities, where large numbers of patients are treated, where the resources are limited and where patients lack the appropriate education and empowerment related to their illness),

5. Late presentations with advanced stage disease, with a number of patients dying of complications during the work up or shortly after a definitive diagnosis is made, and without receiving any specific therapy or an adequate number of courses of specific therapy,

6. Lack of 'state of the art' therapy, or limitations regarding optimal therapy in the public sector setting (due to cost and other issues related to accessibility).

All these challenges need to be looked at, in order to provide realistic and potential solutions, as we move forward to improve the healthcare of our society and our nation.

5.0. CHAPTER 5: CONCLUSION

Multiple Myeloma (MM) is the second most common haematologiocal malignancy encountered in adults at CHBAH, after NHL. HIV has reached endemic proportions in our patient population, and is impacting on the lymphomas, leukaemias and MM. This study was undertaken to better characterize the association between HIV-1 sero-positivity and MM in our patient population. The key findings in this study were:

1. An increase in the number of MM patients from 165 (2006-2010) and 168 (2011-2015), to 268 (2016-2020), in the latter 5 years of the study. A corresponding increase in HIV seropositivity of 10.9% (2006-2010) and 10.1% (2011-2015), to 18.3% (2016-2020) in the latter 5 years of the study,
2. A younger mean age of 50 years, with a female predominance of 1.5:1,
3. More than half the patients (54.7%) had an ECOG PS ≥2,
4. Bone pain and anaemia were the dominant clinical features,
5. A higher proportion of cytopenias, including leucopenia, neutropenia and thrombocytopenia were noted,
6. Plasmacytomas were evident clinically in 29% of patients and radiologically in 52% of patients,
7. Biochemical features of note were: hypercalcaemia in 56% of patients, renal dysfunction in 33% of patients, hypoalbuminaemia in 65% of patients and an elevated B2M level in 96.3% of the patients. The median CD4 count was 367 cells/ul, with a range of 23-964 cells/ul. Approximately a quarter of the patients (26.1%) had a CD4 count <200 cells/ul,
8. IgG isotype (74%), was the most common subtype of MM,
9. Lytic lesions were found in up to 77% of the patients on CT scan, with vertebral compression fractures being present in 77% of patients on MRI,
10. Most patients had advanced stage of disease, with DS stage III in 92% of the patients and ISS stage III in 70% of the patients,
11. Specific therapy in the form of chemotherapy (various combinations of cytotoxics, corticosteroids and immunomodulatory drugs such as thalidomide, etc.) was administered to 76% of the patients, 34% had radiotherapy and only 6% had an ASCT,
12. Despite the use of cART and specific therapy, the overall outcome was poor, with a median survival of 5.64 months (Interquartile range 0.82-19.24 months),
13. Survival was statistically significantly better in those who received chemotherapy and/or radiotherapy compared to those who only received supportive care only (p=<0.001) and those who had ISS stage I and II disease, compared to ISS stage III disease (p=0.006), and

14. Although survival was better in those who had a higher CD4 count (≥200 cells/ul versus <200 cells/ul) (p=0.081), and those who achieved at least a PR versus <PR (p=0.108), these two parameters were not statistically significantly different.

5.1. FUTURE RECOMMENDATIONS

Although chronic antigenic stimulation and immunodeficiency in HIV-1 sero-positive individuals may contribute to an increased risk of MM, it is unclear whether the association between the two diseases in our patients, is causal or coincidental. Nevertheless, what is apparent is that this association is increasing (18% in the latter five years of the study). As such, we need to create awareness of this, so that the patients can be recognized, diagnosed and treated timeously, in order to improve the prognosis and outcomes of the patients.

It is clear from this study, that MM in association with HIV-1 sero-positivity presents in younger individuals, with a female predominance, with typical and characteristic features of bone pain, anaemia, lytic bone lesions, vertebral compression fractures, hypercalcaemia, renal dysfunction, as well as more frequent extramedullary manifestations such as plasmacytomas, predominance of an IgG isotype, advanced stage disease and inferior outcomes. Future recommendations should include:

Continued efforts to prevent, minimize and lessen the burden of HIV, together with early initiation of antiretroviral therapy, recognition of, and aggressive and optimal management of complications of the disease.

Education with regard to the key clinical manifestations of MM, early suspicion of the diagnosis and timeous referral to a tertiary or specialized centre, so that treatment can be initiated as soon as possible.

Appropriate follow up of the patients to assess response to treatment and to detect early relapse or progression of the disease.

Efforts to improve accessibility of ‘state of the art’ and novel therapies for public sector patients.

Efforts to increase the number of patients who require an ASCT, as part of consolidation treatment.

Furthermore, prospective, multicentre studies need to be undertaken to optimally manage HIV-1 sero-positivity in association with MM.

In principle, these patients should be offered the same treatment options as HIV-1 sero-negative individuals, with the proviso that every attempt is made to achieve optimal virological suppression and immune reconstitution.

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APPENDICES

APPENDIX A: HREC APPROVAL

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 7th September 2020

TITLE OF PROJECT:

A fifteen-year review of Multiple Myeloma in HIV seropositive patients at Chris Hani Baragwanath Academic Hospital.

UNIVERSITY: Witswatersrand

Principal Investigator: Dr J Baxter

Department: Internal Medicine

Supervisor : Prof Moosa Patel, Dr Atul Lakha

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 7/9/2020

Approved/~~Not Approved~~
Hospital Management
Date: 08/09/2020

APPENDIX B: EXTENSION OF STUDY APPROVAL

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2021/07/14

Dr JMN Baxter
School of Clinical Medicine
Department of Medicine
Division of Internal Medicine
Medical School
University

Sent by e-mail to: baxterjayson@gmail.com

Dear Dr Baxter

Re: **Protocol Ref No:** M201170
Protocol Title: *A Fifteen-year Review of Multiple Myeloma in HIV seropositive patients at Chris Hani Baragwanath Academic Hospital*
Principal Investigator: Dr JMN Baxter

Thank you for your letter of 2021/07/07.

I confirm that we have noted and approve of your proposal to add patient records for the years 2019 and 2020 to your study. You might want to check whether the Faculty of Health Sciences (Sandra.Benn@wits.ac.za) will require a change to your study title, since it presumably no longer covers just a "fifteen year" period.

Thank you for keeping us informed.

Yours Sincerely

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

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

APPENDIX C: THE IMWG DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA

Symptomatic
M-protein in serum or urine
BM plasma cell ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma
Evidence of end-organ damage that can be attributed to the underlying lymphoproliferative disorder (MM) (CRAB-hypercalcaemia, renal impairment, anaemia, bone lesions)
≥ 1 biomarker of malignancy • clonal BM plasma cells ≥ 60% • involved: uninvolved serum FLC ratio ≥ 100, with iFLC> 100mg/l • > 1 focal lesion on MRI studies
BM, bone marrow, FLC, free light-chain, iFLC, involved free light-chain, MRI, magnetic resonance imaging

APPENDIX D: THE DURIE-SALMON STAGING SYSTEM FOR MULTIPLE MYELOMA

Stage	Features
I	All of the following: Haemoglobin>10 g/dl Serum calcium normal (< 12mg/dl) Bone radiograuphy normal (scale 0) or solitary bone lesion or plasmacytoma only Low monoclonal Ig production rate: IgG < 5 g/dl; IgA < 3 g/dl; Bence-Jones protein < 4g/24h
II	Neither stage I nor stage III
III	One or more of: Hb < 8.5 g/dl Calcium > 12 mg/dl Advanced lytic bone lesions (scale 3) High monoclonal Ig production rate: IgG > 7g/dl; IgA > 5 g/dl Monoclonal urinary protein > 12 g/24h
Sub-classification according to renal function	A: Relatively normal (serum creatinine < 2.0 mg/dl) B: Abnormal (serum creatinine ≥ 2.0 mg/dl)

APPENDIX E: INTERNATIONAL STAGING SYSTEM FOR MULTIPLE MYELOMA

Stage	Criteria	Median survival (months)
I	Serum B2-microglobulin < 3.5 mg/l Serum albumin ≥ 3.5 g/dl	62
II	Not stage I or III (serum B2-microglobulin 3.5-5.5 mg/l with any albumin level or albumin < 3.5 g/dl and B2-microglobulin < 3.5 mg/l	44
III	Serum B2-microglobulin ≥ 5.5 mg/l	29

APPENDIX F: DATA COLLECTION SHEET

Demographics:

Study Number	
Gender	Male ☐ Female ☐
Age at presentation	Age: _____ years
Date of diagnosis	DD: MM: YYYY:
Date of haematology referral	DD: MM: YYYY:
Performance status (initial)	0 ☐ 1☐ 2☐ 3☐ 4☐
Ethnic group	B ☐ W ☐ C ☐ A ☐ Other: _____

History:

Symptoms	Yes	No	
Bone pain	☐	☐	Site/s: Back/spine ☐Ribs ☐ Humerus☐Femur ☐ Other: ☐Site/s: _____
Fever	☐	☐	
Loss of weight	☐	☐	Amount (kg): _____ Time (weeks-months): _____
Night sweats	☐	☐	
Fatigue	☐	☐	
Bleeding	☐	☐	Site: _____
Comorbidities (see below for details)	☐	☐	HIV ☐ TB☐ Other ☐ Details: _____
Hyperviscosity	☐	☐	
Plasmacytoma	☐	☐	Site/s: _____
Weakness (Motor)	☐	☐	Lower limbs ☐Upper limbs ☐
Sensory changes / Neuropathy	☐	☐	Details: _____ _____

Hypertension	☐	☐	
Diabetes	☐	☐	
Cardiac / Pulmonary / Renal disease	☐	☐	Details: _____ _____
If HIV seropositive	☐	☐	CD4 count: _____ Date diagnosed: _____
If positive, is patient on cART?	☐	☐	Date Commenced: _____ Type: _____
If prior or current TB	☐	☐	Pulmonary/Extrapulmonary TB? _____ When was TB diagnosed? _____ Duration of treatment? _____

Examination:

Signs	Yes	No	
Pallor	☐	☐	
Pedal oedema	☐	☐	
Jaundice	☐	☐	
Lymphadenopathy	☐	☐	Site/s: _____ _____
Plasmacytoma	☐	☐	Site/s: _____ _____ Details: _____ _____
Infection	☐	☐	
Hepatomegaly	☐	☐	Size below costal margin _____cm
Splenomegaly	☐	☐	Size below costal margin _____cm

Bleeding	Petechiae ☐ Purpura ☐ Ecchymoses ☐ Mucosal ☐	☐ ☐ ☐ ☐	
Neurological deficit	☐	☐	Details: _____
Other relevant clinical findings, if present	☐	☐	

Chest X Ray:

Normal ☐ Abnormal ☐

Abnormality	Details
a) Bony disease (lytic lesions/fractures)	_____
b) Lung parenchymal disease	_____
c) Pleural disease	_____
d) CTR/ Cardiac disease	_____

Other X Rays:

Normal ☐ Abnormal ☐

(lytic lesions, pathological fractures, vertebral compression fractures, osteopenia)

Site: _____ Abnormality/ies: _____

1) _____

_____

2) _____

_____

3) _____

_____

4) _____

_____

MRI Scan:

Normal ☐ Abnormal ☐

1) Signal intensity changes _____

_____

Bony disease (as above) _____

_____

_____

_____

_____

_____

_____

3) Soft tissue masses _____

_____

_____

_____

_____

_____

4) Spinal cord compression Yes ☐ No ☐

Site: _____ Details: _____

CT scan / PET-CT scan:

Yes ☐ No ☐

If done, comment on abnormalities:

_____

_____

_____

_____

_____

_____

If abnormal, comment on the presence of:

i. Nodal disease _____

_____

ii. Lung parenchymal disease _____

_____

iii. Pleural disease _____

_____

iv. Bony disease _____

_____

v. Cardiac disease (CTR/chamber enlargement) _____

_____

Bone Marrow:

% plasma cells _____

_____

Morphology of plasma cells _____

_____

Other comments _____

_____

_____

_____

Ploidy:	Aneuploidy ☐ ☐	Hyperdiploidy☐	Hypodiploidy☐
CD 38	☐ Yes (Positive)	☐ No	%/ Brightness _____
CD 138	☐	☐	%/ _____
CD 56	☐	☐	%/ _____
MUM-1	☐	☐	%/ _____
Ki-67	☐	☐	%/ _____
CD 20	☐	☐	%/ _____
Kappa	☐	☐	%/ _____
Lamba	☐	☐	%/ _____
Other	☐	☐	_____

Cytogenetics:

Date: _____ Abnormality: _____

	Yes	No	Dates
t(4;14)	☐	☐	_____
t(14;16)	☐	☐	_____

t(14;20)	☐	☐	_____
t(11;14)	☐	☐	_____
13q	☐	☐	_____
17p	☐	☐	_____
TP 53 mutations	☐	☐	_____
Ip/Iq abnormality	☐	☐	_____
Complex karyotype	☐	☐	_____
Other	☐	☐	_____

Other - Histology e.g. Plasmacytomas

Date: _____ Site: _____

Findings: _____

_____

Light chain restriction: _____

Other: _____

Stage of disease:

Salmon-Durie: _____

_____

ISS: _____

Other: _____

Treatment:

a) Supportive care:	Yes	No	Details
Allopurinol	☐	☐	_____
Analgesics	☐	☐	_____
Antibiotics	☐	☐	_____
Bisphosphonates	☐	☐	_____
ESA's	☐	☐	_____
Dialysis	☐	☐	_____
IVIg	☐	☐	_____
Other	☐	☐	_____

b) Specific modality: Drugs used (dose, no. of cycles)

Induction	☐	☐	CVAD: _____
			Thalidomide: _____
			Melphalan: _____
			Decadron: _____
			Other: _____
Consolidation	☐	☐	Auto SCT: _____
			Other: _____
Maintenance	☐	☐	Thalidomide: _____
			Corticosteroids: _____
			Other: _____

c) Relapse:

1) How long after initial treatment _____	☐	☐	How treated: _____ _____ _____
2) _____	☐	☐	_____
3) _____	☐	☐	_____

d) Response:

i. To initial treatment (duration of response; best response)

sCR/CR/PR/SD/PD/other:

_____

_____

_____

_____

ii. Relapse and further response

(Best response and duration of response)

_____ _____

_____ _____

iii. Relapse

_____

_____

iv. Relapse

_____ _____

_____ _____

v. Relapse

_____ _____

_____ _____

Outcome:

Alive ☐ Deceased ☐ Lost to follow up ☐

Date last seen: _____

Response status at last visit: _____

If deceased:

Survival _____months (from date of histological diagnosis to death)

Cause/s of death _____

If lost to follow up:

Date last seen_____

Status of disease at last visit (type of remission/response, active disease):

PR Yes ☐ No ☐

CR/sCR	Yes	☐	No	☐
PD	Yes	☐	No	☐
SD	Yes	☐	No	☐

5.2. APPENDIX G: FLOW SHEET OF BLOOD RESULTS

FLOW SHEET OF BLOOD RESULTS

	Normal Values	Initial presentation	After initial response	At relapse	As at last date seen
Date					
WCC	4-11 x 10^9/l				
Hb	♀ 14-18g/dl ♂ 12-16g/dl				
Hct	♀ 0.4-0.52 l\l ♀ 0.35-0.48 l/l				
MCV	80-100 fl				
PLT	150-400 x 10^9/l				
Neutrophils	2-7.5 x 10^9/l				
Lymphocytes	1-4 x 10^9/l				
Monocytes	0.2-0.8 x 10^9/l				
Basophils	0-0.1 x 10^9/l				
Eosinophils	0-0.5 x 10^9/l				
Smear					
% Plasma cells					
Rouleaux formation					
Reticulocytes	0.2-2%				
RPI	1-2				
ESR					
Sodium	135 – 147 mmol/				
Potassioum	3.3 – 5.3 mmol/l				
Chloride	99 – 113 mmol/l				
CO2	18 – 29 mmol/l				
Urea	2.6 – 7.0 mmol/l				
Creatinine	60 – 120 μmol/l				
Glucose	4.1 – 11.1 mmol/l				
Calcium	2.05 – 2.56				

	mmol/l				
Magnesium	0.65 – 1.1 mmol/l				
Phosphate	0.8 – 1.4 mmol/l				
CRP					
LDH	100 - 200 U/l				
B2 Microglobulin	0.7 – 1.8 mg/l				
Uric acid	0.22 – 0.45 mmol/l				
HIV status					
HIVVL					
CD4	0.2 – 1.0 g/l				
Hepatitis A					
Hepatitis B					
Hepatitis C					
Iron	10 – 30 µmol/l				
Transferrin	2.0 – 3.6 g/l				
%saturation	25 – 50%				
Ferritin	30 – 400 µg/ml				
Vitamin B12	145 – 637 pmol/l				
Serum Folate	5 - 20 µg/l				
Red cell folate	924 – 3337 mmol/l				
Glucose	2.2 – 3.9 mmol/l				
Bilirubin	0 – 21 µmol/l				
Direct bilirubin	0 – 6 µmol/l				
Total protein	60 – 86 g/l				
Albumin	35 – 52 g/l				
Globulin	25 – 30 g/l				
ALP	40 – 120 U/l				
GGT	0 – 60 U/l				
ALT	5 – 40 U/l				
AST	5 – 40 U/l				
Immunoglobulins					
IgG	7.0 – 16.0 g/l				

IgA	0.7 – 4 g/l				
IgM	0.4 – 2.3 g/l				
Paraprotein					
SFLC					
K	3.3 – 19.4 mg/L				
ƛ	5.7 – 26.3 mg/L				
Ratio	0.25– 1.65				
Other					

5.3. APPENDIX H: TURN-IT-IN REPORT

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Division of Haematology, Department of Medicine, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg
Chris Hani Road, Diepkloof, Soweto. Tel: +27 11 9339377, Fax: +27 11 9339449, email: moosa.patel@wits.ac.za

11 September 2023

The Chair

Postgraduate Studies Committee

Faculty of Health Sciences

University of the Witwatersrand

Re: Turn-it-in report: Dr Jayson McNeil Baxter (0702132K) – MMed: A 15-Year Review of Multiple Myeloma in HIV-1 sero-positive patients at Chris Hani Baragwanath Academic Hospital: A retrospective review'

I have reviewed the Turn-it-in report of Dr Baxter's MMed dissertation. The report identifies a similarity index of 31%. Much of this similarity relates to recurring terminology, classifications and definitions which are standardized. Also, a number of studies have been summarized, in which the factual and exact information regarding numbers and percentages had to be included. This was unavoidable, based on the nature of the information that was included in the dissertatation. The other information which bears a similarity has been appropriately and correctly referenced.

Thank you

Yours sincerely

Moosa Patel MBChB, FCP(SA), MMed(Wits), FRCP(Lond.), PhD(Wits)

Emeritus Professor of Clinical Haematology, Department of Medicine, Chris Hani Baragwanath Academic Hospital and the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Final Mmed Jayson Baxter-1.docx

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