

**A retrospective review of the demographic profile,  
disease activity, co-existent co-morbid disease and  
treatment in established rheumatoid arthritis at a  
tertiary center clinic**

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## Declaration

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## **Dedication**

I dedicate this work to my parents Mr. and Mrs. G Singh for their commitment and unwavering support in all my endeavors.

## **Acknowledgements**

I wish to express my sincerest gratitude to my supervisor Dr. F Paruk for her guidance, wisdom and patience. Her mentorship and tireless assistance has been truly invaluable. I also wish to thank Prof. N Magula for her ongoing support.

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## Overview of thesis

Rheumatoid arthritis (RA) is one of the most common forms of chronic inflammatory arthritis and often results in joint damage, physical disability and premature mortality. The incidence of RA is increasing in developing countries, especially in urban areas amongst lower socio-economic groups. There is a dearth of data on non-communicable diseases such as RA in South Africa (SA) as resources and research is concentrated on addressing the high burden of communicable diseases due to human immunodeficiency virus (HIV) and tuberculosis (TB) compounded with addressing high maternal and infant mortality rates. Therefore despite the severity and resultant functional disability, RA remains poorly understood and often mismanaged.

This study aims were to understand the natural history of patients with RA treated in a public sector tertiary clinic. The objectives of this retrospective study are to describe the demographic profile, disease activity, drug management and comorbid disease profile in patients with established RA attending a dedicated rheumatic clinic at King Edward VIII Hospital in Durban.

A retrospective chart review was conducted of the files of all RA patients attending the arthritis clinic at King Edward VIII Hospital, for a period of at least ten years. The demographic data, serological status, current disease activity, functional class, co-morbid diseases, and treatment were recorded on a structured data collection tool.

In this study, Indians comprised the majority (n=81, 58.7%) followed by Blacks (n = 51, 36.9%). All the patients met the clinical criteria for RA on the initial visit, with 73 (63.5%) having a positive rheumatoid factor (RF). Synovitis was still observed in 35.5% of patients at their last visit and in these patients the C-reactive protein remained elevated at  $\geq 16$  mg/dL ( $p < 0.0001$ ). Radiographs showed a significant deterioration in terms of erosions between the two time points ( $p < 0.021$ ). Hypertension was the most frequent co-morbid disease seen in 96 (69.6%) patients.

There were several limitations as this was a retrospective study and therefore there were a number of files that had incomplete or missing data. The clinical assessment of disease was performed by several clinicians and inter-observer variability was another shortcoming. Further the study was limited to the public sector only and potentially excluded other ethnicities and therefore may also not be an accurate reflection of natural history of RA in SA.

This study highlights the need for better and tighter RA control in the SA public sector and the need for prospective studies with adequate representation of all ethnic groups to evaluate the challenges faced in delivering an effective rheumatology service in SA.

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## Chapter 1: Literature Review

### Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown aetiology characterized by a symmetrical, peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and untreated results in joint damage, physical disability and premature mortality (1, 2).

Autoimmune in nature, it is a systemic disorder associated with several extra-articular manifestations including but not limited to lung involvement, peripheral neuropathy, vasculitis, eye changes and haematological abnormalities. Rheumatoid nodules, one of the most typical diagnostic features of RA, are found in 20-30% of patient who always will have a positive test for rheumatoid factor (1, 2).

### Pathogenesis

While the exact cause of RA remains elusive, an infective cause from an ubiquitous agent in a genetically susceptible host may be the underlying trigger. Additionally although several causative agents and their products (e.g. heat shock proteins) have been linked to RA via a process of molecular mimicry, most notably Epstein-Barr virus, to date no compelling evidence has emerged (1).

In contrast, the pathogenic mechanisms of synovial inflammation in RA are better understood, and is thought to be driven by immune dysregulation, inflammation and a breakdown in self-tolerance (3). A key pathway in RA inflammation, is the overproduction and overexpression of tumour necrosis factor (TNF), which drives both synovial inflammation and joint destruction leading to excessive production of interleukin-6 (IL-6), an important pro-inflammatory mediator. Additionally, IL-1 is also abundantly expressed in RA and promotes activation of leucocytes, endothelial cells, chondrocytes and osteoclast in the pannus itself. The release of inflammatory mediators from the synovium results in malaise, fatigue and elevated levels of acute-phase reactants (APR) (1, 3, 4)

The rheumatoid synovium, the pathognomic feature of disease in RA is hyperplastic and infiltrated by lymphocytes and mesenchymal cells. Fibroblast like synoviocytes resident in these synovial joints show abnormal behaviour and proliferate with expression of high levels



of cytokines and chemokines that promote a permissive micro-environment that sustains T - cell and B - cell survival and ongoing cartilage damage and erosion to underlying bone (4).

This inflammatory response results in auto-antibody production and rheumatoid factor (RF) auto-antibodies are found in 75 - 80% of RA patients at some time during the course of their disease. Immunoglobulin (Ig), IgM and IgA rheumatoid factors are pathogenic markers directed against the Fc fragment of IgG (1). High titres are predictors of a severe disease and correlate with extra-articular manifestations. Although the levels of RF may fluctuate with disease activity, RF is not used as a measure of disease activity (5).

Additionally, increasingly important types of antibodies, against citrullinated peptides (CCP) have been recognized. Anti-cyclic citrullinated peptide antibodies (ACPA) are produced in the liver and are directed against deaminated peptides (6). Studies suggest that ACPA have a greater sensitivity (50-75%) and specificity (>90%) than RF and are of particular diagnostic benefit in patients who test RF antibody negative. Anti-cyclic citrullinated peptide are better predictors of poor prognostic features such as progressive joint destruction, erosive disease and high levels of disease activity (7, 8). Additionally ACPA are a predictive tool for RA, and may precede the clinical manifestations of disease by up to 14 years.

Individuals with RA susceptibility genes including HLA-DRB1, who are also smokers are at a significantly higher risk of developing ACPA (9). Distinct differences are observed in the synovium of patients who test positive for RF and anti-CPP, compared to autoantibody negative patients. Auto-antibody positive disease has increased lymphocytes whereas those with ACPA negative RA are more likely to have fibrosis and increased thickness of the synovial layer (10).

Although an important diagnostic marker, RF and ACPA are found in approximately 5% and 1.5% of normal individuals respectively, and therefore alone are insufficient for the diagnosis of RA (5, 6).

In the last two decades, the understanding of the pathogenesis of RA has significantly advanced with the identification of disease related genes and deciphering of the involved molecular pathways (1, 4)

There is a strong genetic correlation seen in RA, with at least a 50% risk of developing the disease being attributable to genetic factors. The concordance rate of RA in identical twins is

12 – 15% and amongst first degree relatives is 2 - 10 times greater than the general population (1).

Recently there has been significant progress in identifying the genetic regions and single nucleotide polymorphisms associated with RA. Currently more than 30 genetic regions are associated with RA, the major ones being PTPN22 and the class II major histocompatibility complex (MHC), the human leucocyte antigen; HLA – DR gene. Further, genetic studies show differences in the ACPA status of patients with RA, related to the number of specific HLA - DRB1 alleles. These HLA alleles share a common motive, an amino acid sequence at positions 70 - 74 in the third hyper-variable regions of the HLA - DRB chain, which is known as the shared epitope (11, 12).

Genetic studies of the HLA - DR alleles show that DR4 is the most common association among patients attending rheumatology clinics in South Africa (SA). A study in 1995, in Durban Blacks of Zulu descent, found a 44% frequency of DR4 in RA patients compared to 10% in controls (13, 14). Similarly studies from Cape Town in Whites, Blacks and patients of Mixed Ancestry also showed a consistent association of HLA – DR4 in all population groups with a relative risk of 3,2 in Whites, 3,9 in Blacks and 3,7 in patients of Mixed Ancestry with RA (15).

### **Environmental risk factors**

Several environmental risk factors are thought to increase the risk of RA, and the best studied amongst them is smoking. Smoking doubles the risk of developing RA, especially women who smoke cigarettes have a nearly 2.5 times greater risk of RA. Interestingly the risk from smoking is almost exclusively related to RF and ACPA positive disease (1).

Other potential environmental risk factors include; alcohol intake, coffee intake, vitamin D status, oral contraceptive use and low socioeconomic status, although supporting evidence for these other factors is weak (16).

Urbanization has also been associated with an increased prevalence of RA, possibly due to the effects of air pollution. A study from the Harvard Medical School found an increased risk of RA in women exposed to traffic pollution and who lived within 50 meters of a road (17). Additionally studies in urban, suburban and rural populations in Taiwan similarly suggest that environmental factors such as air pollution may affect RA susceptibility in individuals who share the same genetic background (18).

## Epidemiology

The peak incidence of the onset of RA is in the fourth decade of life and the disease is three times more common in women than men, with prevalence increasing with age in both sexes. The highest prevalence is seen in women older than 65 years, suggesting hormonal factors may play an important role (1).

Rheumatoid arthritis affects approximately 0.5 - 1% of adults in the developed world and there is significant geographic and ethnic variation within countries (Figure 1) (1). In the Native American Pima Indians of North America, an extremely high prevalence has been shown of up to nearly 7% in some studies. In contrast, other population studies from Africa and Asia show lower prevalence rates in the range of 0.2 – 0.4% (19).

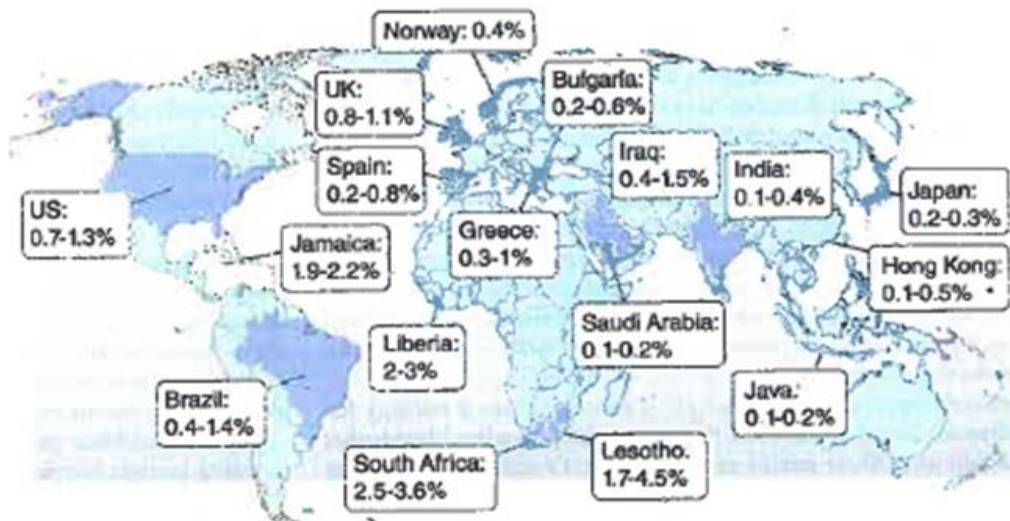


Figure 1 Global prevalence rates of rheumatoid arthritis (1)

There are limited studies from Africa on RA and these are from a few countries (SA, Nigeria and Uganda). Traditionally RA was thought to be rare in Africa and to have a milder disease course compared to the developed world, however recent studies suggest an increasing incidence of RA in Africa.

A systematic literature review of the burden of RA in Africa showed a prevalence of 0.36% in the 1990's, which translated to a burden of 2.3 million affected individuals. Based on the above prevalence rates it is expected that by 2019, this figure would increase to 0.42% and the burden to 4.3 million people in Africa. This figure, however, is thought to be an

underestimation as it is calculated using hospital based studies which under-report the prevalence by about six times in comparison to population based studies (20).

The exact incidence of RA in Africa presently remains uncertain but there is increasing evidence that the prevalence of RA is increasing in the indigenous populations of East, Central and South Africa although it remains rare in West Africa (20, 21).

Studies from SA, have shown a higher disease activity and prevalence in the Black urban community of Soweto (0.9%) compared to rural communities; Tswana in Western Transvaal (0.1%), Xhosa in Eastern Cape (0.68%) and Sotho's in Lesotho (0.3%). Interestingly, the prevalence rate has been documented to be 0% amongst the Venda peoples. The reasons for the lower rates of RA in rural African populations remains unclear but it supports environmental factors in the pathogenesis of RA (22-24).

The mean age of onset of RA at 36.6 years (range 17 - 54) in SA Blacks is significantly lower than the 44.2 years reported in Caucasians, but similar to the younger mean age of onset of 33 years reported in Nigerians (25, 26).

Similar to developed countries, there is a greater female preponderance of RA in developing countries, however the ratio is much higher and more than double that reported in the Western world. Tikly et al, in Soweto (2003), found a gender ratio of 6.9:1 amongst established RA patients, which is consistent with observations from Latin America and other developing countries (27-29).

### **Clinical manifestations and systemic consequences of rheumatoid arthritis**

Rheumatoid arthritis causes a polyarticular symmetrical inflammation of the joints, tendons and bursae and presents with pain, swelling and early morning joint stiffness (EMS), usually lasting more than one hour. The earliest affected joints are usually the small joints of the hands and feet. Constitutional features frequently accompany joint involvement and include fatigue, fever, weight loss and lymphadenopathy (2).

In approximately one third of patients there may be an atypical presentation with either an initial mono / oligo-articular involvement or an asymmetrical pattern of disease.

Extra-articular manifestations may occur during any stage of RA in up to 40% of patients. Predictors for extra-articular involvement include smoking, sero-positive RF disease and early onset of severe physical disability (30). Amongst the most frequently observed extra-

articular manifestations are subcutaneous nodule, secondary Sjogren's syndrome, pulmonary nodules and anaemia (1). A study from Cape Town in 1989, confirmed a similar spectrum of extra-articular disease in Black patients with anaemia being the most common finding (40%), followed by subcutaneous nodules (25%) and keratoconjunctivitis sicca (10%) (13).

Osteoporosis secondary to chronic inflammation and glucocorticoid therapy is a frequent complication in RA and independently affects functional capacity, apart from increasing the fracture risk. International studies have confirmed a 22% higher incidence of osteoporosis of the hip or lumbar spine in RA patients compared with the general population (31), whilst another study demonstrated a significantly increased risk of osteoporotic fracture in RA patients independent of CS use (32).

Local studies from Cape Town in premenopausal women with RA, also show that generalized bone loss is a systemic feature of RA, with significant vertebral and femoral bone loss seen in young patients with an overall prevalence of osteopenia of 6% (33). Further, the bone loss at the spine and femur is aggravated by CS therapy (33). Studies also show that the prevalence of metacarpal osteopenia was 55% in young RA patients and that this may be a useful potential measure of disease activity in RA patients (34).

Comparative studies amongst patients receiving high dose CS therapy for systemic lupus erythematosus (SLE) to low dose CS therapy for RA demonstrated that metacarpal bone mass was significantly higher in patients with SLE than RA. This was despite the larger cumulative doses of CS for longer periods in SLE suggesting that in RA, bone loss is a feature of disease severity rather than of CS therapy (35).

### **Radiological changes**

Radiographs although useful in diagnosis are more useful to detect disease damage and disease progression. Untreated RA will lead to bone erosions in 80% of patients within one year of diagnosis. Erosive bone disease is associated with prolonged inflammation and is a measure of disease activity (36). Juxta-articular erosions characterize progressive established RA and are usually irreversible. Erosions are readily identified by conventional radiography and two typical erosions are sufficient to confirm the diagnosis, while extensive ongoing damage on radiographs suggests poorly controlled disease (37). Radiographs should be repeated every two years in patients with remission or with low disease activity (38).

Recently ultrasound (US) and magnetic resonance imaging (MRI) are being increasingly used, as they can assess both reversible and irreversible structural changes compared to conventional radiographs. The advantages are improved sensitivity in detecting synovitis, joint space narrowing and erosions earlier. The addition of power colour doppler ultrasound allows for the detection of increased joint vascularity indicative of inflammation (39).

Magnetic resonance imaging (MRI) allows a three-dimensional perspective and precise assessment of the bony and soft tissue structures within a targeted joint. The main 'activity' findings detected by MRI include synovitis, tenosynovitis and bone marrow oedema (BME), while the 'damage' findings include bone erosions and joint space narrowing. Tamai et al. reported a scoring system using baseline ACPA and / or RF, MRI findings of symmetrical synovitis and MRI BME and / or bone erosion to predict early RA with 82.5% sensitivity and 84.8% specificity. However with MRI the RA criteria are not uniformly defined and this together with cut-off values in MRI scoring systems requires further research (40).

### **Laboratory investigations**

The severity of RA is determined by a combination of clinical examination, radiological findings and use of biologic markers which include APR, the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP). The APR describes the local and systemic inflammatory and repair processes that accompany inflammation (37).

Although the ESR level is widely used and it correlates with disease activity, and it is useful for monitoring therapeutic response; its use is limited by the size, shape and number of red blood cells as well as other plasma constituents such as immunoglobulins all of which also affect ESR levels in any given patient (41).

The CRP is a more objective measure of disease activity and is the preferential acute phase marker, however an increase in both CRP and ESR is a stronger indication of radiological progression than that of CRP alone (42). Vd Heijde et al, showed that an absence of radiographic joint progression after two years could be correctly predicted in 83% of the patients using a combination of disease activity at presentation; ESR, CRP, disease activity score (DAS) and DR4 and RF positivity (43). Additionally, Yildirim et al, reported significant correlations between serum APR levels and disease activity based on the DAS 28 (a composite disease activity score that combines information about swollen and tender joints, the APR and general health in RA patients) (44).

These markers of systemic inflammation have also been found to independently add to the risk for cardiovascular (CV) death in RA. Observational studies show an increased risk of cardiovascular disease (CVD) that correlates with the activity and duration of the RA as measured by APR (45).

Other disease activity markers include a low serum haemoglobin (46) and Mody et al, (1989) reported anaemia as the most common extra-articular manifestation of RA in Black South Africans (13). It is postulated that the anaemia is mediated by inflammatory cytokines, particularly IL-6 (47). Similarly, a reactive thrombocytosis associated with active RA is most likely due to the pro-inflammatory effects of IL-1 $\beta$  and IL-4 (48).

### **Diagnostic criteria**

The understanding of the pathogenic mechanisms of RA has led to the development of new therapeutic drugs and the understanding that early therapeutic intervention improves clinical outcomes and reduces disability. In an attempt to ensure early recognition of RA in 2010, the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) developed a new classification system for RA, with the goal of identifying patients who would benefit from early effective intervention as the previous ACR1987 criteria were limited by poor sensitivity and specificity for classification of patients with early inflammatory arthritis as having RA (49).

The new diagnostic classification compared to the old 1987 criteria improve sensitivity in detecting early disease by focusing on the early features of disease that are associated with persistent and / or erosive disease. In an attempt to improve the recognition of RA, in 2010, the new criteria were revised to be more specific about the joint involvement, serology, APR and symptom duration as shown in Table 1 (49).

**Table 1. ACR/EULAR 2010 Rheumatoid Arthritis Classification Criteria (49)**

		Score
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, thumb IP, MTP, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive anti-CCP antibodies ( $\leq 3$ times ULN)	2
	High-positive RF or high-positive anti-CCP antibodies ( $> 3$ times ULN)	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	$\geq 6$ weeks	1

**Note:** These criteria are aimed at classification of newly presenting patients who have at least one joint with definite clinical synovitis that is not better explained by another disease. A score of  $\geq 6$  fulfills requirements for definite RA.

**Abbreviations:** ACPA, anti-citrullinated peptide antibodies; CCP, cyclic citrullinated peptides; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IP, interphalangeal joint; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RF, rheumatoid factor; ULN, upper limit of normal.

**Source:** D Aletaha et al: *Arthritis Rheum* 62:2569, 2010.

### Disease activity assessment

The success of therapy for RA relies on the goals of treatment to be specified in advance and to assess response timeously and objectively. There are several methods of scoring disease activity in RA, where the clinical examination of tender and swollen joints, global assessments and laboratory investigations are combined into a composite score (50, 51).

Common indicators of disease activity in RA include:

- Pain
- Duration of morning stiffness
- Fatigue
- Measures of function
- Swollen and tender joint counts
- Patient and evaluator global assessment of disease activity
- ESR and CRP

The three validated scores currently in clinical use in SA are the DAS-28, the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) (51), and these are summarized in Table 2.



**Table 2. Composite measures of disease activity (37)**

Composite measures of disease activity.

	Method of assessment	Definition of clinical remission
Disease Activity Score (DAS)	Calculated using a mathematical formula comprising 3 variables: <ul style="list-style-type: none"> <li>• number of swollen joints (out of 44 specified joints),</li> <li>• Ritchie articular index (evaluation of the tenderness of 53 joints, on a scale of 0–78),</li> <li>• laboratory markers (CRP or ESR).</li> </ul> DAS using 4 variables may also be calculated, incorporating patient global health assessment (recorded on a visual analogue scale).	Score < 1.6
DAS based on 28 joints (DAS28)	Calculated using a mathematical formula comprising: <ul style="list-style-type: none"> <li>• number of swollen joints (out of 28 specified joints),</li> <li>• number of tender joints (out of 28),</li> <li>• Patient global health assessment (visual analogue scale),</li> <li>• laboratory markers (CRP or ESR).</li> </ul>	Score < 2.6
Clinical Disease Activity Index (CDAI)	The sum of 4 variables: <ul style="list-style-type: none"> <li>• number of tender joints (out of 28),</li> <li>• number of swollen joints (out of 28),</li> <li>• physician or evaluator's global assessment of disease activity (visual analogue scale of 0–10),</li> <li>• patient global assessment of disease activity (visual analogue scale of 0–10).</li> </ul>	Score ≤ 2.8
Simplified Disease Activity Index (SDAI)	The sum of CDAI plus CRP (in mg dl <sup>-1</sup> ).	Score ≤ 3.3

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; ACR, American College of Rheumatology; EULAR, European League against Rheumatism.

These scores allow classification of RA disease into a state of remission or low, moderate or high disease activity and thereby provide a simple tool for assessing disease at each visit to guide therapeutic decisions. The level of disease activity is an important indicator of functional outcome, joint damage and radiographic progression.

The SDAI and CDAI have been validated in several cross sectional cohorts and are accurate reflections of disease activity, sensitive to change and feasible to perform in all clinical settings. Further, the Pearson correlation analysis showed excellent correlation between the DAS28, SDAI and CDAI scores and patients disease activity levels (52, 53). The advantage of the CDAI is that it is the only composite score that does not incorporate an APR and can therefore be conducted at any time.

Additionally the ACR response criteria is a set of standard criteria which measure clinical change in response to treatment. The ACR 20 response measures at least a 20% improvement

in the number of tender and swollen joints and a 20% improvement in at least three of the following five areas : the APR, the physician's global assessment of disease status, the patients assessment of pain, the patients assessment of function and the patients global assessment of disease status. Similarly the ACR 50 and 70 will report a 50% and 70% improvement in the above parameters (50).

Both active and established RA have a substantial effect on physical functioning, therefore instruments designed to measure physical functioning are useful indicators of disease severity.

Measuring functional ability in chronic arthritis is challenging and the importance of standardized measures of functional capacity have been recognized. The criteria for evaluation of such instruments include methods for quantification, reliability, validity and precision. There is no one preferred method and almost all of the current instruments measure health status, disease activity and functional status (54).

In a local study comparing functional changes to changes in measures of disease activity it was noted that functional disability is related to activity and not chronicity. A number of tools have been used previously including the Lansbury systemic index, Keitel functional index and the Ritchie articular index to measure overall function in RA i.e. disease activity and function (55).

The Health Assessment Questionnaire (HAQ) is a comprehensive tool designed to assess patient disability, discomfort, medication, side effects, cost and mortality and has is recently used in clinical practice in the present time (50). Of these components, only the HAQ Disability Index (HAQ-DI) is used frequently in clinical trials and clinical practice. It evaluates a patients' ability to perform activities of daily living through their self-reported answers to 20 questions designed to assess upper or lower extremity use (50).

The modified ACR 1991 global functional scale has been shown to correlate closely with the HAQ. It is a useful and accepted score to describe the global functional consequences of RA especially with regard to assessing physical and work disability (56).

Functional class, although not sensitive enough to detect small changes in functional capacity, is a frequently used tool for the purpose of classifying patients at entry into clinical trials (57). The 1991 ACR revised version of the 1949 American Rheumatism Association

(ARA) criteria for the classification of global functional status were validated by Hochberg et al, in 1992 and the differences are tabulated in Table 3 (56).

**Table 3. Comparison of the ARA 1949 and ACR 1991 ‘Global Functional Scale (56)**

ACR 1991 Classification	ARA 1949 Classification
<p><b>Class I</b>            Completely able to perform usual activities of daily living: self-care, vocational (work, school, homemaking) and avocational (recreational and leisure)</p>	<p>Complete functional capacity with ability to carry on all usual duties without handicaps</p>
<p><b>Class II</b>            Able to perform usual self-care and vocational activities, but limited in avocational activities</p>	<p>Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints</p>
<p><b>Class III</b>            Able to perform usual self-care activities, but limited in vocational and avocational activities</p>	<p>Functional capacity adequate to perform only few or none of the duties of usual occupation or of self-care</p>
<p><b>Class IV</b>            Limited in ability to perform usual self-care, vocational, and avocational activities</p>	<p>Largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no selfcare</p>

<sup>a</sup>In contrary to the ‘old’ ARA criteria, the ‘new’ ACR criteria have been validated.

### **Rheumatoid arthritis and associated co-morbid disease**

The association between RA and non-communicable disease (NCD) is well established and on average the established RA patient has two or more co-morbid conditions, which play a pivotal role in RA management and outcomes. The NCD’s associated with RA are cardiovascular disease (CVD), infections, lymphoproliferative malignancy, gastrointestinal disease and osteoporosis (58).

The greater the number of co-morbid illnesses, the higher the medical costs, subsequent disability and mortality risk. Michaud and Wolfe in their seminal report on “Comorbidities in rheumatoid arthritis” noted that; “It should be the responsibility of the rheumatologist to take this and the risk of additional conditions into account when treating the patient”(59).

Bishri et al, found in a relatively small study that the most common co-morbid conditions in RA were hypertension (35.9%), diabetes (30.9%) osteoporosis (25.8%) and dyslipidaemia (19.4%) (60). Similarly Solomon et al. (1995) found that hypertension was the most common comorbidity and affected 50% of RA patients in both the SA public and private sector (61).

Accumulating evidence suggests that atherosclerosis and CVD are truly inflammatory disorders sharing a common pathophysiology with synovial inflammation and pannus formation that characterize RA. Indeed it has been suggested that atherosclerosis and CVD be considered “extra-articular manifestations” of RA. Overlapping pathogenic features of the two diseases include the predominant role of pro-inflammatory cytokines (e.g. TNF-alpha and IL-6), elevated serum levels of APR (CRP, fibrinogen and serum amyloid), abnormal endothelial cell function and neoangiogenesis. This unchecked cellular dysregulation is postulated to account for the increased prevalence and severity of coronary calcification in RA and therefore it is not surprising that CVD is the leading cause of death in patients with RA (58, 62, 63).

Cardiovascular disease risk in RA is similar to CVD risk in diabetes mellitus (DM) with both appearing to be of equal frequency and severity (63).

An additional risk factor in RA is that some of the medications used for treatment may have dual effects on risk for CV morbidity. This is exemplified by the use of corticosteroids which although they decrease CV complications in RA by decreasing inflammation, they also increase CV risk by promoting pro-atherosclerotic lipid profiles, hypertension and insulin resistance (63).

It is now widely accepted that atherosclerosis in RA is associated with both traditional CV risk factors such as age and hypertension, as well as non-traditional risk factors of chronic inflammation (64).

### **Management of rheumatoid arthritis**

The EULAR “treat to target” guidelines recommend remission as the target of therapy in all patients with RA regardless of early or established disease. These guidelines, however, do recognize that a state of low disease activity may be an acceptable alternative target, especially in patients with long standing disease and the aim of treatment is minimization of disease activity with disease modifying anti-rheumatic drugs (DMARDs) that slow or prevent structural progression of RA (30, 65).

Achieving and maintaining low disease activity in the shortest time period using single or combination DMARD's, improves long term outcomes and is a cost effective strategy compared to older, more gradual approaches of initiating DMARD therapy (66).

The most commonly used DMARD's in the past were gold, penicillamine and minocycline; which all produced a slow response with an associated high level of toxicity, resulting in low compliance rates. Further due to their varying degrees of success and inconsistent clinical efficacy they are no longer used (1, 30).

Hydroxychloroquine (HCQ) and sulphasalazine (SSZ) were subsequently introduced and were used for early mild disease or as adjunctive treatment (1). Hydroxychloroquine is not available in SA and chloroquine is used instead, which local anecdotal experience shows as having equivalent efficacy to hydroxychloroquine. However neither HCQ nor chloroquine have been shown to delay radiographic progression and are therefore not considered to be a true DMARD, while SSZ has been shown in randomized controlled trials to reduce radiographic progression of disease (1, 67, 68).

The introduction of methotrexate (MTX) and its widespread use in the late 1980's, dramatically changed the therapeutic landscape in RA. Methotrexate is regarded as the anchor drug in RA, it is effective as monotherapy and is the benchmark for testing efficacy and safety of all new DMARDs. Methotrexate is administered as weekly therapy, usually between 7.5 to 25mg weekly (30).

Several studies show good long term compliance and remission on MTX and Choi et al, showed a 60% overall reduction in mortality in subjects on MTX (69). Additionally a systematic literature review on the long term safety of MTX monotherapy in patients with RA demonstrated good tolerability of the drug and favourable long term safety (69-72). Data on MTX use and compliance show that approximately 60% of patients receiving high dose MTX (12.5 mg per week) still use the drug six years later, and in a separate twelve year follow-up study 53% of patients continued to take MTX (irrespective of any periods of temporary discontinuation) (73).

Methotrexate has several adverse effects, which may be dose dependent. Adverse effects of MTX may be minor (e.g. nausea) or more serious (e.g. hepatotoxicity, blood dyscrasias and interstitial lung disease). Monitoring of adverse effects include pre-treatment screening and subsequent safety recording of full blood counts and liver function tests throughout the course of therapy (1).

Although the treatment of choice, if MTX cannot be tolerated, or results in adverse reactions or is contraindicated, SSZ or leflunomide are available alternative drug choices.

Leflunomide is a pyrimidine synthesis inhibitor and clinical trials show clinical efficacy similar to that of MTX as monotherapy or in combination therapy (1).

Disease modifying anti-rheumatic drugs may be combined to improve efficacy (67, 68). The combination of MTX, SSZ and HCQ – is termed triple therapy. A randomized trial comparing combination therapy with single drug therapy with MTX in early RA, showed combination therapy was more effective without increasing toxicity risk in inducing RA remission in early disease (68).

### **Biological agents**

The introduction of the biological DMARDs, which are intravenous proteins that target cytokines and cell surface molecules, has revolutionized the treatment of RA. They may be broadly classified into TNF inhibitors and non – anti - TNF agents and these include B cell targeted therapy against CD 20 (rituximab), T cell co-stimulation blockade with the fusion protein (abatacept) and IL-6 receptor inhibition (tocilizumab) (1).

Studies have shown that the combination use of MTX and biological agents makes clinical remission and radiographic non-progression a realistic and achievable goal in patients with both early disease and severe RA (66).

The Early Rheumatoid Arthritis (ERA) trial which compared etanercept vs. MTX monotherapy in patients with early erosive RA found that although both drugs were associated with a reduction in disease activity and radiological joint damage, the ACR20 response in the etanercept group was significantly higher than for MTX at 24 months (72% vs. 59%, respectively,  $p = 0.005$ ) (74).

In contrast, the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study showed that the combination of etanercept and MTX was significantly better in reducing disease activity, improving functional disability and retarding radiographic progression compared with MTX or etanercept alone. Importantly 75% of patients achieved an ACR20 in the methotrexate only group compared to 85% of patients in the combination group who achieved ACR20 ( $p = 0.005$ ). This finding reiterates the efficacy and use of MTX as first line therapy especially in a resource limited setting (75).

In SA, the RA treatment guidelines for use of biological therapy recommend a six month trial of at least three synthetic DMARDs (including MTX, unless contraindicated) before

biological agents can be initiated. This approach is based on the evidence that up to one third of all patients will achieve low disease activity on synthetic DMARD therapy alone, and the significant cost implications of biological agents in both the public and private health care sector (51).

### **Surgical procedures for rheumatoid arthritis**

Surgical procedures play an important role in patients with long standing and advanced RA in improving pain and disability. The surgical options chosen depend on both the stage of disease and also the size and type of the joint involved. In general, total joint arthroplasty is preferred for large joints with severe disease, such as the knee, hip, shoulder or elbow (1).

Total joint replacement (TJR) of the knee and hip accounts for a significant proportion of the cost of the disease (76). In a study by Wolfe and Zwillich (1998) it was estimated that 25% of all patients with RA between 1970 and through to the 1990 required TJR surgery (77).

In SA, although surgical treatment is widely available, there are significant delays in joint replacements in the public health care sector due to resource constraints. Local studies have shown that delays in initiating medical treatment lead to a higher number of surgical interventions with up to 49.2% of RA patients requiring at least one surgical procedure. Significantly, of these 15.6% had a replacement arthroplasty of one or more of the four major weight bearing joints (78).

However, with the introduction of newer treatment options the need for joint surgery has decreased substantially in the developed world. The number of total hip and knee joint arthroplasties in patients' with RA in Ireland decreased from 1995 to 2010, despite substantial increases in these procedures among the general population (79). Skytta et al, had similar findings in their study comparing trends in total knee replacements (TKR) in RA and osteoarthritis (OA), showing clearly reduced annual incidence of TKR in RA while steadily increasing incidence amongst OA patients. Both of these studies and several other reports suggest improving long term outcomes in RA (80, 81).

### **Expert care**

The treatment of RA has been revolutionized in the last three decades and in association with improved drugs is the recognition that the involvement of a rheumatologist improves care and outcomes. The initial and continued care of patients with RA by a rheumatologist is

associated with better disease outcomes and decreased functional disability, compared with care rendered primarily by other clinicians. Further the importance of tight control, utilizing a treat-to-target strategy is best developed and maintained by an expert physician which ensures optimal patient outcomes (21, 51, 82).

Unfortunately the number of rheumatologist in Africa is inadequate in comparison to the population. There are only 72 registered rheumatologists in SA for the 55 million population as of October 2016 (83) and there is no data on the distribution between public and private sector or the actual number of physicians in active practice. There are also no accurate published data on the number of rheumatologists in Africa.

### **Long term outcomes in rheumatoid arthritis: functional and social outcomes**

Rheumatoid arthritis has a significant impact on health-related quality of life, and is associated with an increase in health care costs and mortality in affected patients compared with the general population. Due to severity of their disease and treatment delays a significant number of patients are unable to continue to work and become dependent on the state for their health care and social welfare support, resulting in an increase in the economic burden(29, 59, 84, 85). In contrast, early recognition and treatment of RA and maintenance of function will result in substantial reduction in the costs to society.

Predictors for poor function include functional status at the onset of the disease, female gender, extent of inflammation, low levels of formal education and low socioeconomic status (86).

Moreover apart from functional disability, RA has psychological effects including impact on overall quality of life and happiness levels. The psychological impact was clearly observed in patients living with RA in Soweto, “The experience of living with RA in a low resource context are similar to those in a mid and high resource contexts, but are exacerbated by poverty and lack of basic services. Pain and social exclusion are some of the key experiences of women with RA living in Soweto”(84).

Mody et al. identified in a study in Kwa-Zulu Natal that pain, stiffness and financial problems were the main problems, emphasizing that clinical and laboratory markers do not describe the full impact of RA and its resultant joint inflammation and deformities (87). The evaluation of the course and outcome of RA by measuring only symptoms and signs of inflammation is



therefore incomplete and a focus on functional disability, psychological problems and associated handicaps with their repercussions is required (84).

### **Prognosis**

Rheumatoid arthritis is a disease with a natural history of severe long term outcomes and is associated with a reduced life expectancy of a median of 10 years in men and 11 years in women (62, 85, 88).

The overall mortality rate is two times greater than in the general population and the leading cause of death is ischemic heart disease. Patients at increased risk for death are those with extra-articular disease manifestations, low socioeconomic status, low education levels, reduced functional capacity and chronic prednisone use (42, 86, 89).

## **Purpose of the study**

Contemporary epidemiological data on the prevalence and incidence of RA in SA is urgently required to improve recognition and care and inform policy making in RA (20).

Importantly there is a need for tighter RA control in the SA public health care sector and Solomon et al, found that RA outcomes were poorer in the public health sector compared to the private health sector and better disease control is urgently required (61).

The long term clinical, functional outcomes and mortality although well established in developed countries are also not well understood in the developing world and these parameters are important in informing future management guidelines. This study aims to examine disease activity and functional outcomes in patients with established RA for greater than ten years in an attempt to improve our understanding of the natural history and management of the disease in a SA in a multi-ethnic population.

## **Specific Objectives**

- Describe the demographic profile of RA patients in a multi-ethnic public health care setting.
- Describe the disease duration and document the proportion of sero-positive and sero-negative RA patients.
- To document the number of patients with active disease after a minimum of 10 years and to determine if standard care of practice are followed.
- To describe disease activity in sero-positive and sero-negative patients with RA.
- Describe the co-morbid disease profile and describe if standard of care received is in keeping with a tertiary institution.
- To document the use of disease modifying anti-rheumatic drugs in this cohort.

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## Chapter 2: Manuscript

### **A retrospective review of the demographic profile, disease activity, co-existent co-morbid disease and treatment in established rheumatoid arthritis at a tertiary center clinic**

#### **Abstract**

#### **Background**

Rheumatoid arthritis (RA) is a chronic inflammatory disease resulting in progressive joint damage and physical disability. Although thought to be rare in Africans, recent studies show an increasing incidence of RA in developing countries. Despite this, there is little attention focused on rheumatic diseases in Africa and there is a paucity of local research.

#### **Aim**

To describe the demographic profile of RA patients at a public sector arthritis clinic and their clinical disease activity, functional outcomes, drug therapy and co-existent co-morbid disease.

#### **Methods**

A retrospective chart review was conducted of the files of all RA patients attending the arthritis clinic at King Edward VIII Hospital, for a period of at least ten years. All RA patients were included provided they were still attending the clinic. Patients with overlap syndromes and other arthritides were excluded. The demographic data, duration of symptoms, initial presentation, serological status, current disease activity, functional class, co-morbid diseases, laboratory results, radiological investigations and treatment were recorded on a structured data collection tool. Data was analyzed using Stata statistical software package. Ethics approval was obtained from the KwaZulu Natal University Bioethical Research Committee.

#### **Results**

The majority of patients were Indians (n=81, 58.7%) followed by Blacks (n = 51, 36.9%). Indian patients (93.8%) were more likely to live in urban areas compared to Black patients (15.6%) (p = 0.000). All patients included fulfilled the 1987 ACR clinical criteria for the



diagnosis of RA, on the initial visit, with 73 (63.5%) having a positive rheumatoid factor (RF). There was a significant association between initial RF positivity and current RF positivity ( $p < 0.0001$ ); indicating that serological status did not change with treatment. Further, a positive association was observed between RF positivity and anti-cyclic citrullinated peptide test ( $p = 0.0120$ ). Synovitis was still observed in 35.5% of patients at their last visit and in these patients the C-reactive protein remained elevated at  $\geq 16$  mg/dL ( $p < 0.0001$ ). Radiographs showed a significant deterioration in terms of erosions between the two time points ( $p < 0.021$ ). The majority of patients were on methotrexate therapy ( $n = 90$ , 65.7%) and 73 patients (53.3%) were on more than one disease modifying anti-rheumatic drugs. Hypertension was the most frequent co-morbid disease seen in 96 (69.6%) patients.

### **Conclusion**

This study found that despite patients having established RA for greater than ten years, a third of patients still had active disease. This highlights the need for a well-defined rheumatology service and early intensive therapy to achieve remission.

## Introduction

Rheumatoid arthritis (RA) was thought to be rare in Africa, however in keeping with the increase in non-communicable diseases (NCDs) seen in developing countries, the prevalence of RA is also increasing (1, 2). Rheumatoid arthritis can result in significant deformities if untreated. Life expectancy is reduced and most patients will experience diminished quality of life (3-6).

There is limited data on the long-term outcomes of RA, and most studies have only included a minority of all patients with RA, and further research in this area is required (3).

In contrast, there have been significant advances in the understanding of the pathophysiology of RA and the advent of potent new biologic therapies which have resulted in a paradigm shift emphasizing the need for earlier recognition, treatment initiation and treat to target remission (7, 8). This strategy has resulted in improved patient outcomes in regard to disease activity and functional class (9-12).

In developing countries, including South Africa (SA), early diagnosis and optimal treatment of RA remain a challenge as the focus of public health care remains on treating communicable diseases (13). This is despite the increasing evidence that the prevalence of RA is rising in sub-Saharan Africa, possibly related to urbanisation, with the lower socio-economic groups bearing the brunt the disease (1, 14).

There are limited epidemiological studies in RA from SA, and only one longitudinal retrospective study on RA, describing the functional outcomes and response to disease modifying anti-rheumatic drugs (DMARDs) (15). Therefore, there are significant gaps in the knowledge of the natural history and outcomes of RA in a local resource constrained setting. This is compounded by a shortage of rheumatologists and prohibitively high costs of newer DMARDs which pose a challenge to delivering rheumatic care (15-17).

This study describes the local experience of treating established RA in a tertiary care centre with respect to long term outcomes, drug management and co-existent co-morbid disease. These findings may be used to review and modify public health care policies, to raise awareness and recognition that early aggressive treatment of RA may result in health care saving and prevent long term disabilities.

## **Methodology**

Ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu Natal (KZN), management of King Edward VIII Hospital (KEH VIII) and the provincial department of Health KZN.

This study was conducted in eThekweni, at KEH VIII hospital which is a tertiary hospital, first established in 1936 during the apartheid government and therefore historically served mainly the Black and Indian population.

A rheumatology clinic was established in the 1980's, and in 2003 when the rheumatology department moved to Inkosi Albert Luthuli Central hospital, this clinic continued to function but under the care of trained medical officers. In April 2015, the clinic once more became a specialist-based clinic.

A retrospective chart review of all patients with a clinical diagnosis of RA was conducted in June 2016. Inclusion criteria for the study were a minimum of ten years disease duration, confirmed diagnosis of RA and current attendance at the clinic. Patients with concomitant connective tissue diseases, or other forms of arthritis were excluded.

The demographic data including age, ethnicity defined according to file and gender were recorded. The date of first visit, duration of symptoms, initial presentation, period of follow up, serological status (rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA), current disease activity, functional class (FC), co-morbid diseases, laboratory results (haemoglobin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)), radiological investigations and treatment were recorded on a structured data collection tool (Appendix 4).

A total of 152 files of patients with established RA were reviewed. Fourteen patients were excluded from the study either because of insufficient clinical data or because only one visit was recorded.

Each file was assigned with a unique study number and the data was captured onto an Excel spreadsheet. Only de-identified data was submitted for analysis. There was no patient contact.

## Statistical Methods

Data was analyzed using Stata version 14 (StataCorp. 2015). Means/medians and frequencies were used to describe the data. Differences in continuous variables between groups were analyzed using the Wilcoxon Mann-Whitney test. Associations between categorical variables were analyzed using the Pearson chi square test or, where expected cell counts were less than 5, Fisher's exact test was instead utilised. Results were considered statistically significant for p-values less than 0.05.

## Results

### Demographic profile: Ethnic, age and gender distribution

The majority of patients were Indian (n = 81, 58.7%) followed by Blacks (n = 51, 37.0%), while Coloureds (n = 5, 3.6%) and Whites (n = 1, 0.7%) made up a minority.

The mean age of the total group was 63.7 years  $\pm$  10.6 years, with a range of 41 to 92 years. There were 120 (87%) woman and only 18 men (13%), and the female to male ratio was 6.6:1. The female to male ratio was higher in Black patients compared to Indians at a ratio of 9.2:1 vs. 7.1:1 (Table 1).

The majority of Indian and Black patients resided in an urban area 63.6%, with only 19.7% and 16.7% living in a peri-urban or rural area respectively. Indian patients were significantly more likely to reside in an urban area compared to Black patients (93.8% vs. 15.7%, p = 0.000).

### Disease history

The mean age of disease onset was 41.7 years  $\pm$  11.0 years, with a similar mean age of onset in both the Indian and Black population group at 41.3 years  $\pm$  9.7 years vs. 42.7 years  $\pm$  12.6 years respectively (p = 0.486) (Table 1).

The median duration between symptom onset and first presentation to an arthritis clinic was 2.0 years with an interquartile range (IQR) of 1 to 4 years. There was no significant difference in time to presentation between urban and rural dwellers (p = 0.934) or between Indian and Black patients (p = 0.420) (Table 1).

The mean duration of established RA in patients was 21.8 years  $\pm$  7.0 years, with similar duration of disease in Indian and Black patients (21.1 years  $\pm$  6.6 years vs. 21.6 years  $\pm$  7.7 years respectively).

The mean follow-up time at the clinic was 17.4 years  $\pm$  6.1 years amongst all patients.

**Table 1. Demographic profile of Indian and Black patients and disease history**

	Indians (n = 81)	Blacks (n = 51)	p-value
<b>Gender, n (%)</b>			
Men	10 (12.3)	5 (9.8)	
Woman	71 (87.7)	46 (90.2)	
Gender ratio F:M	7.1:1	9.2:1	0.654
<b>Age (years) mean (<math>\pm</math>SD)</b>			
Current	62.8 $\pm$ 10.2	64.2 $\pm$ 11.3	0.463
Age at Onset <sup>1</sup>	41.3 $\pm$ 9.7	42.7 $\pm$ 12.6	0.486
<b>Residence, n (%)</b>			
Urban	76 (94.0)	8 (15.7)	
Peri-urban	4 (5.0)	22 (43.1)	
Rural	1 (1.0)	21 (41.2)	0.001
<b>Disease duration<sup>1</sup>, mean (<math>\pm</math>SD)</b>	21.1 $\pm$ 6.6	21.6 $\pm$ 7.7	0.677
<b>Time (years) delay before presentation<sup>1</sup>, median (IQR)</b>	2 (1-4)	2 (1-5)	0.420
<b>Follow up (years) at arthritis clinic<sup>2</sup>, mean (<math>\pm</math>SD)</b>	17.1 $\pm$ 6.6	18.0 $\pm$ 5.5	0.446
<sup>1</sup> Based on n = 75 Indians, n = 49 Blacks			
<sup>2</sup> Based on n = 77 Indians, n = 50 Blacks			

### **Pattern of disease distribution, deformities and extra-articular manifestation**

The majority of patients (83.7%) had a symmetrical poly-articular pattern of disease with small joint involvement in a rheumatoid distribution at their initial presentation and only 16.4% of patients had evidence of established hand deformities. In contrast, 78 patients (67.2%) had hand deformities at their last visit ( $p = 0.006$ ).

Extra-articular features documented at initial visit were specifically rheumatoid nodules and sicca symptoms ( $n = 17$  and  $n = 22$  respectively). The most common manifestation was sicca symptoms (19.5%), which remained significantly positive at the last visit ( $p=0.000$ ).

Subcutaneous nodules were found only in 17 patients on the initial visit and only four patients had rheumatoid nodules at last visit.

### **Serological status**

An initial RF serology was only available in 115 patients files, and the majority were positive for RF ( $n = 73$ , 63.5%). There was no significant difference in the serological status between Indians and Blacks (62.7% vs.65.1%;  $p = 0.841$ ) at the initial visit.

The RF and ACPA tests were repeated during the last year in 77 and 65 patients respectively. There was a significant positive association between the presence of the two serological tests (74% RF vs. 76.9% CCP;  $p = 0.012$ ). Further a positive ACPA test correlated significantly to urban residence ( $p = 0.019$ ) and was significantly more common in the Indian than in the African population group (57.4% vs. 42.6%;  $p = 0.041$ ).

Only nine patients that were RF negative at the initial visit, tested RF positive at the last visit, indicating a significant association between initial RF and current RF ( $p < 0.0001$ ).

### **Disease activity**

Disease activity was measured using early morning stiffness (EMS), active synovitis as documented in clinical notes and acute phase reactants (APR).

The mean duration of EMS decreased significantly from 120.4 minutes  $\pm$  89 minutes at the initial visit to 44 minutes  $\pm$  55.4 minutes ( $p = 0.000$ ) at last visit.

The number of patients with active synovitis had also decreased significantly on reassessment (81% vs. 35.5%;  $p < 0.001$ ) and no significant difference was noted between RF or ACPA serological status of patients and disease activity ( $p = 0.113$  and  $p = 0.513$  respectively).

Although a significant decrease in synovitis was observed clinically, the mean ESR was not significantly different between the two time points (54.3 mm/hr.  $\pm$  28.4 mm/hr. vs. 51.8 mm/hr.  $\pm$  35.7 mm/hr.;  $p = 0.478$ ) (Table 2).

C-reactive protein measurements were not routinely performed in the arthritis clinic initially and therefore have only been documented in the last two years. The median CRP, measured at the last clinic visit was 9 mg/dL (IQR 5mg/dL - 24mg/dL) (Table 2). Further, unlike the ESR findings, a CRP  $\geq$  16 mg/dL was significantly more often observed in patients who had clinically active disease compared to patients in remission ( $n = 47$  vs.  $n = 87$ ;  $p < 0.0001$ ).

A significant increase in the mean haemoglobin (11.7 g/dL  $\pm$  1.4 g/dL vs. 12.2 g/dL  $\pm$  1.5 g/dL respectively;  $p = 0.003$ ) (Table 2) and decrease in the mean platelet count (363.5 cells  $\times$   $10^9$ /L vs. 296 cells  $\times$   $10^9$ /L;  $p < 0.0001$ ) was observed between initial and latest haematological results which also was associated with a decrease in disease activity.

**Table 2. Laboratory investigations at initial and last visit**

	<b>Initial visit</b>	<b>Last visit</b>	<b>p-value</b>
<b>Erythrocyte sedimentation rate (mm/hr.), mean (<math>\pm</math>SD)</b>	54.3 $\pm$ 28.4	51.8 $\pm$ 35.7	0.478
<b>C-reactive protein (mg/dL), median (IQR)</b>		9 (5 - 24)	-
<b>Haemoglobin (g/dL), mean (<math>\pm</math>SD)</b>	11.7 $\pm$ 1.4	12.2 $\pm$ 1.5	0.003
<b>Platelets (<math>\times</math> <math>10^9</math>/L), mean (<math>\pm</math>SD)</b>	363.5 $\pm$ 106.8	296.0 $\pm$ 83.8	< 0.0001

### **Functional class**

A significant association was noted between FC across the two time points ( $p < 0.001$ ) (Table 3).

Patients who presented with FC I and FC II were more likely to remain in the same class or show a deterioration in their functional status. At the initial visit, 54 patients were in FC class 1, while at the last visit only 30 were still in FC I and 18 patients had moved to FC II. Similarly of the 38 patients who were initially in FC II, 19 patients remained in FC II and 13 had deteriorated to a FC III at current visit.

In contrast, patients who presented with a poorer FC, FC III and FC IV were more likely to improve from first visit and have a higher FC at the current visit. Of the 19 patients in FC III at first visit, 11 had improved to FC II and only 7 remained in FC III at current visit. All 3 of the patients who started in FC IV at first visit were now in FC III.

**Table 3. Functional class at the initial and last visit**

	<b>Initial Visit</b>	<b>Last Visit</b>			
<b>Functional Class</b>		<b>I</b>	<b>II</b>	<b>III</b>	<b>IV</b>
<b>I</b>	<b>54</b>	30	18	6	0
<b>II</b>	<b>38</b>	5	19	13	1
<b>III</b>	<b>19</b>	1	11	7	0
<b>IV</b>	<b>3</b>	0	0	3	0
<b>Total</b>	<b>114</b>	36	48	29	1

### **Radiographs**

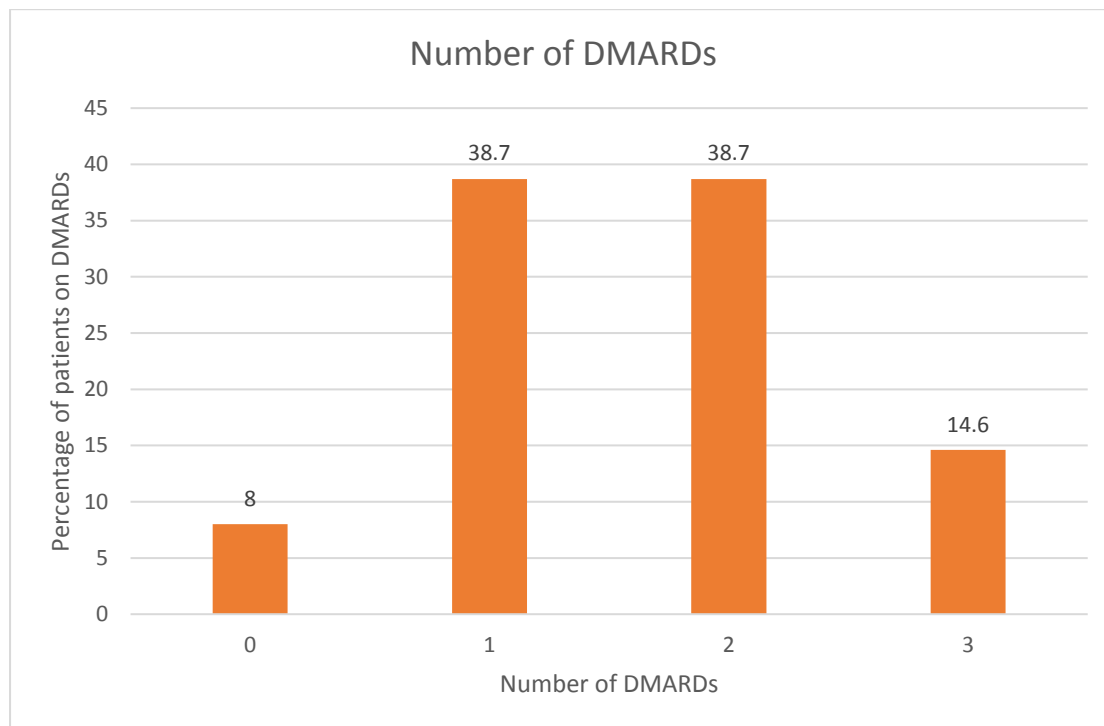
Radiographs were available for comparison in only 42 patients between the two time points. Thirty five (83.3%) patients had RA changes at initial visit with 17 (40.5%) having erosions. A significant deterioration was observed on repeat radiographs and all radiographs now showed typical RA changes and erosions were present in 83.3% of radiographs ( $p = 0.021$ ).

### **Medical management**

The pattern and use of DMARDS (methotrexate (MTX), salazopyrine (SSZ), and chloroquine (CQ)) is described in 137 patients with only one patient excluded due to missing data. A minority, 20 patients (14.6%) were on triple therapy, 53 patients (38.7%) each were either on



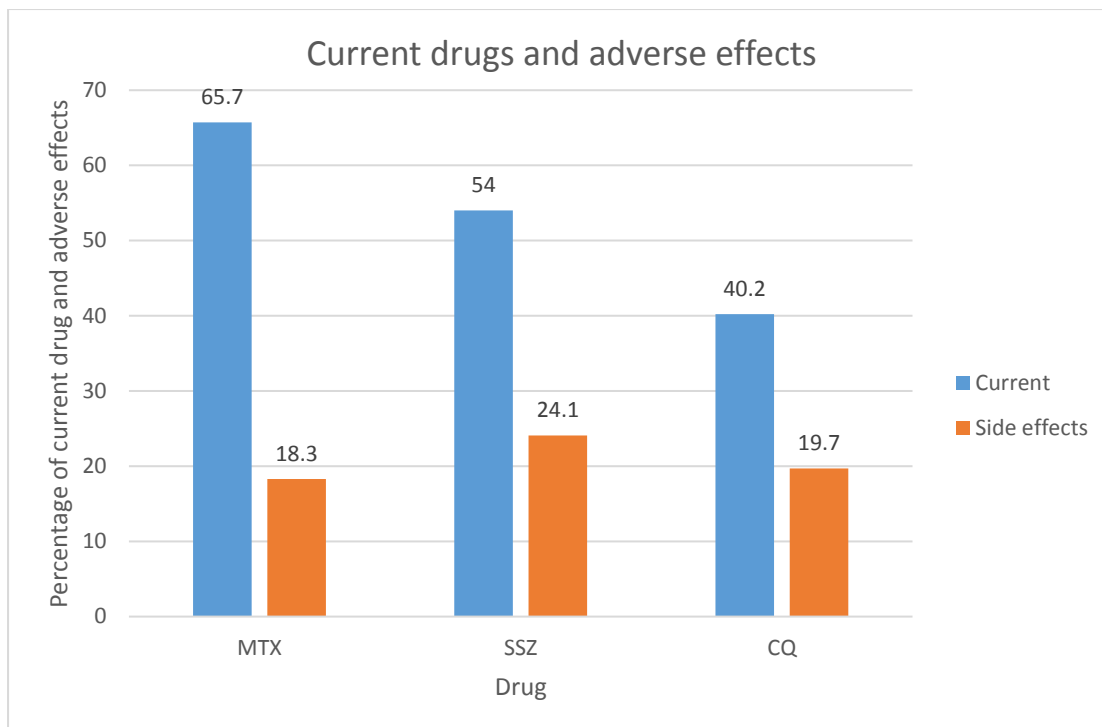
one or two agents respectively and 11 patients (8%) were not on any DMARD therapy (Figure 1).



**Figure 1. Percentage of rheumatoid patients on disease modifying anti-rheumatic drugs**

The majority of patients 90 (65.7%) were on MTX therapy with only 18 patients (13.1%) having never been on MTX. The median dose of MTX was 17.5 mg (IQR 15 mg-20 mg) weekly and the mean number of years on MTX therapy was 12 years  $\pm$  4.2 years (Figure 2).

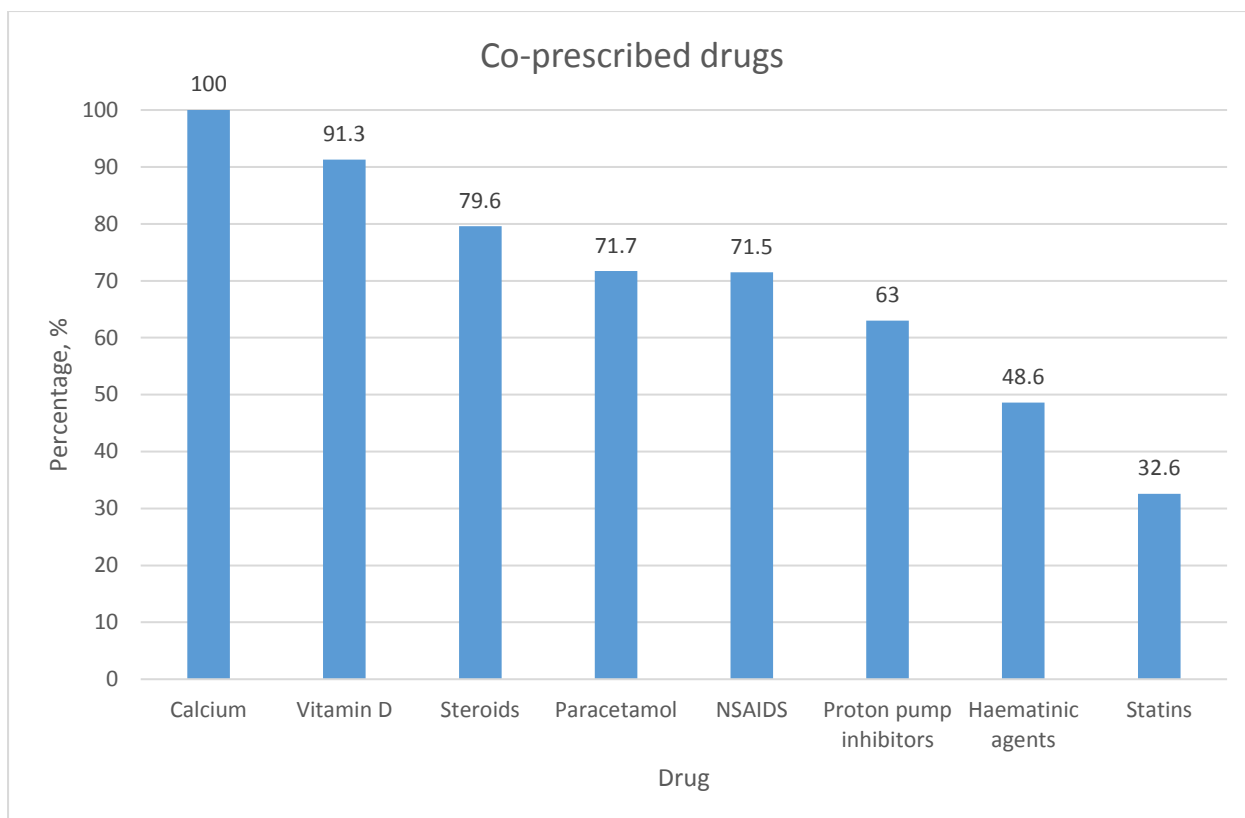
There were 74 patients (54%) on SSZ and 55 patients (40.2%) on CQ either alone or in combination with MTX. Side effects were seen most commonly with SSZ and SSZ was discontinued in 33 (24.1%) patients, this was followed by CQ discontinuation in 27 (19.7%) patients and lastly by MTX discontinuation in 25 (18.3%) patients.



**Figure 2. Current drug use and adverse effects resulting in cessation of drug therapy (%)**

Non-steroidal anti-inflammatory drugs and corticosteroids were the most frequently prescribed adjunctive therapy in 109 (79.6%) and 98 (71.5%) patients respectively. Paracetamol was prescribed in 71.7% and tramadol in 37% of patients (Figure 3).

Bone protective drugs, calcium and vitamin D were prescribed in the majority with 100% and 91.3% of patients on these drugs respectively. Other frequently prescribed drugs included proton pump inhibitors (63%), oral iron supplements (48.6%) and statins (32.6%) (Figure 3).



**Figure 3. Co-prescribed drugs in rheumatoid arthritis patients (%)**

### **Coexistent co-morbid disease**

The most frequent co-morbid condition was systemic hypertension (n= 96, 69.57%) and only 29 (21%) patients had diabetes mellitus. Although 32.6% of patients were receiving statin therapy only 114 patients had confirmed fasting lipogram results with 27 (23.7%) patients meeting the diagnosis of dyslipidemia.

A minority of patients 7 (5.2 %) had a diagnosis of human immunodeficiency virus (HIV) infection, subsequent to the initial visit. Bone mineral densitometry (BMD) test results were only available in 38 patients as the hospital DXA machine has not been functional for greater than two years. The majority of RA patients tested (79%) patients had osteoporosis as defined by a World Health Organization osteoporosis classification.

Osteoarthritis (OA) either primary or secondary was noted to be present if documented on clinical examination and / or if reported on radiographic features. Osteoarthritis findings were noted in 91 patients' current clinical notes and the majority of patients (n=89, 87.8%) had osteoarthritic changes.

There were no significant differences in hypertension, diabetes mellitus, HIV, osteoporosis or OA between Indian and Black patients but dyslipidemia was significantly more common in Indian patients (Table 4).

**Table 4. Coexistent co-morbid disease in Indian and Black patients with established rheumatoid arthritis**

	<b>Indians</b>	<b>Blacks</b>	<b>p-value</b>
	<b>n (%)</b>	<b>n (%)</b>	
<b>Systemic Hypertension</b>	56 (69.1)	36 (70.6)	0.860
<b>Diabetes Mellitus</b>	22 (27.2)	7 (13.7)	0.069
<b>Dyslipidemia<sup>1</sup></b>	22 (32.8)	5 (11.6)	0.012
<b>HIV</b>	3 (3.8)	4 (7.8)	0.318
<b>Osteoporosis<sup>2</sup></b>	23 (82.1)	6 (75.0)	0.653
<b>Osteoarthritis<sup>3</sup></b>	50 (98.0)	36 (97.3)	0.818
<sup>1</sup> Based on n = 67 Indians, n = 43 Blacks			
<sup>2</sup> Based on n = 28 Indians, n = 8 Blacks			
<sup>3</sup> Based on n = 51 Indians, n = 37 Blacks			

## **Surgery**

A total of 41 (29.7%) patients had an orthopedic procedure or arthroplasty. The mean number of procedures was  $1 \pm 0.63$ , and knee replacement surgery was the most frequently performed procedure with 63.4% of patients having at least one total knee replacement.

A further 14.6% of patients had hip replacement surgery and 12.2% had arthroscopy performed. Only one patient each had any of the following procedures; ulnar styloid excision, carpal tunnel release and forefoot correction.

## Discussion

The epidemiology and natural history of RA is well established in developed countries, but there are few studies from Africa. This is one of the first studies to report RA outcomes in the Indian and Black population in SA, albeit limited to those attending the public sector for care.

In this study the mean age of disease onset was  $41.7 \pm 11.0$  years which is consistent with studies from Africa, Asia and Latin America which show a younger mean age at disease onset of  $\leq 40$  years (14, 18, 19) almost 10 years younger than Caucasians.

Similarly the gender ratio of female to male at 6.6:1 is much higher than 2-3:1 reported from the USA and Europe (20) and is consistent with earlier SA studies by Mody et al, who found a ratio of 3.7:1 (18) and more recently Tikly et al who reported a female to male ratio of 6.9:1 in Blacks (15). This higher female to male ratio is also seen in Latin America where women are far more frequently affected with a ratio of 7 - 8:1 (19).

Although RA is more commonly seen in urban population, the high percentage of Black patients from a rural area is most likely explained on the basis of the apartheid racial segregation laws that existed in SA pre-1994. These laws affected Indians to a lesser degree (21). Additionally, there are several studies from SA that support a rural-urban gradient in RA distribution (22-24). The influence of urbanization has also been observed in Taiwan (25). The reason for an increased risk in urban areas is poorly understood but exposure to traffic pollution has been postulated to increase the likelihood of RA in industrialized regions (26).

In the last decade, studies have clearly shown that established RA is more difficult to treat and one is unlikely to attain the same outcomes as with early treatment (27-29). In this study, duration of disease before referral was 3.9 years, which is about one year longer than that reported by Tikly et al (15), in a Soweto population. Further the investigators showed that a delay of greater than two years in referral for specialist care contributed to a poorer functional outcome even after three years of treatment. The reasons for late presentation may include lack of recognition of RA by primary care physicians and inadequate access to health care (15, 30-32).

The diagnosis of RA in this study was based on the American College of Rheumatology 1987 (ACR) criteria (33) which included a positive RF which is seen in 60 - 90% of all RA

patients, depending on severity of disease and the isotype measured (34). Consistent with this 63.5% of patients in this study had a positive test for RF.

Additionally there was a significant association between the initial RF and the last RF test result suggesting that the RF status in our cohort did not change with therapy. Further, the failure to observe any significant association between RF and the ACPA tests positivity with clinical disease activity, is in keeping with current recommendations that repeated testing of these serum autoantibodies adds no additional value to ongoing patient management (35).

Although ACPA which is more specific than RF, was not available two decades ago, studies show a close correlation in the sensitivity of RF and more recent second generation ACPA tests (34, 36, 37). This study showed a significant correlation between the sensitivity of the two tests suggesting that RF could be still used as a screening test in resource limited settings.

Additionally although ACPA was significantly more common in Indians, the frequency was not higher than the general population or even from studies from India (38). In contrast the higher incidence of ACPA in urban areas is in keeping with studies that suggest RA prevalence is common in urban areas (24, 25).

In contrast to the study in Black South Africans by Mody et al, subcutaneous nodules were found in a low percentage in this study while sicca symptoms tended to be commoner, possibly as this was mixed a racial group (18).

Further in this study, despite patient being on treatment for almost two decades, one third of patients still had active synovitis at last visit which is not congruent with current treatment aims in RA (39, 40). Possible reasons for continued disease activity include that disease scores such as the Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) were not used, and follow up annual radiography, and regular laboratory monitoring of disease activity were not routinely performed (anecdotal evidence from experience in clinic) which assist in treating to target and optimizing drug therapy (40).

A study from the Gauteng Region Early Arthritis registry showed that inadequate drug therapy is a possibly an important determinant of ongoing disease activity. Hodkinson et al, found that less than one third of indigent patients with early RA (<2 years duration) achieved low disease activity at one year on traditional agents. Interestingly it was observed that failure to control disease early was a marker of persistent disease activity and patients who did not

show an adequate response to DMARDS at six months were unlikely to show further improvement at 12 months (17).

Further the importance of tight control, utilizing a treat-to-target strategy, with a goal of remission or low disease activity is challenging in state clinics where the number of patients seen are usually large and where patients are generally assessed at three monthly or longer intervals (16).

In addition to clinical assessment, CRP and ESR are used in composite disease scores. Although the ESR showed no significant decrease over time, CRP correlated well with the clinical assessment confirming its usefulness in assessing RA as it is not influenced by age, sex, biochemical variations of red blood cells and immunoglobulins (40-42).

Anemia and thrombocytosis, have been consistently reported in the literature and are associated with disease activity (43, 44). In keeping with this there was a significant increase in the mean haemoglobin and decrease in the mean platelet count over the two time points which correlated significantly with the decrease in disease activity. Additionally Hodkinson et al, in a South African study among indigent patients showed that a lower haemoglobin level and increased platelet count were poor prognostic factors (17).

The aim of early RA treatment is to prevent joint deformity and radiographic progression which adversely affects long-term outcome (3-5, 40). Although a significant decrease in EMS was observed in the study following commencement of treatment, to the contrary, established hand deformities were observed in a significantly greater number of patients at the last visit, once more underpinning inadequate disease control. Further, significant changes were observed on the limited radiographs performed supporting findings that radiographic progression occurs early, is progressive, correlates well with cumulative disease activity and may even occur in patients in clinical remission (4, 45). It is now understood that radiographic monitoring is critical in disease monitoring, observing the progression of previously existing joint damage and assessing new joint abnormalities to ensure delivery of optimal care (46).

Additionally the aim of treatment is to restore functional activity and it is established that untreated RA leads to a decline in functional status (3). Paradoxically in this study, patients with better FC were more likely to deteriorate, while those with poorer functioning improved. A possible explanation is that historically patients with severe disease were treated more

aggressively and DMARDs were withheld in mild-moderate disease until there was clear evidence of joint damage or bone erosions (27).

Despite patients initially not being aggressively treated, over time except for a small minority, DMARDs were prescribed in all patients and most patients were on combination DMARD therapy with MTX by their last visit. This study, similar to other studies confirmed the clinical efficacy and tolerability of MTX in RA even at relatively high doses (47-50).

In contrast the ongoing use of prednisone amongst 71.5% of patients is concerning as long term observational studies have associated worsening functional outcome and mortality rates with prednisone therapy (51).

The use of prolonged corticosteroids also add to underlying risk of osteoporosis seen in RA. The prevalence of osteoporosis, despite only a small percentage of patients having a DXA scan in this study, is consistent with other studies in that >75% of patients tested had osteoporosis (52, 53).

Apart from osteoporosis, several other NCDs are associated with RA, and this study confirmed hypertension as one of the most common co-morbidities observed (16, 54). Rheumatoid arthritis is an independent risk factor for atherosclerotic disease and together with traditional risk factors, patients with established RA have an increased cardiovascular (CVS) mortality rate. It is therefore ideal that holistic management should be offered at a single treatment point (54-56).

Surgery in our study was lower compared to the developed world, possibly due to limited access to surgical procedures and lack of resources (14, 15). In contrast developed countries are showing declining rates of surgery due to improved treatment options (57, 58).

### **Study limitations**

This was a retrospective study and therefore there were a number of files that had incomplete or missing data. Also due to the long time period under review there are inconsistencies in data that relate to the use of laboratory tests and details on combination DMARD therapy and lack of access to newer therapies. Further the clinical assessment of disease was performed by several clinicians and inter-observer variability is a shortcoming, and a composite disease activity score such as the CDAI or SDAI was not used to measure disease activity. The study was also limited to the public sector only and potentially excluded other ethnicities and



therefore may also not be an accurate reflection of natural history of RA in SA. Additionally this was a relatively small sample size and long term outcome of mortality was not assessed.

### **Conclusion**

There are well described differences in RA epidemiology in terms of age, gender and urbanization in developing countries. This study similarly found that woman are significantly more likely to have RA, patients present at a younger age and urbanization is significantly associated with positive ACPA status. Despite a significant decrease in synovitis after DMARDS were commenced, at least one third of all patients still had active disease and radiographs showed significant progression highlighting the need for better and tighter RA control in the South African public sector.

Prospective studies with adequate representation of all ethnic groups are required to evaluate the challenges faced in delivering an effective rheumatology service and to look at the role of newer biologic therapies. Additionally long term studies that evaluate measures of damage with regard to disability are needed. This information will assist in planning local policies in a resource limited setting.

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## **Appendix 1: Study protocol**

**Title of Study**

A retrospective review of the demographic profile, disease activity, co-existent co-morbid disease and treatment in established rheumatoid arthritis patients in a tertiary/regional hospital.

**Purpose of Study**

Rheumatoid arthritis (RA) is a chronic inflammatory multi-systemic disease targeting the synovium, that untreated can result in significant deformities, leading to impaired functional outcome and major disability (1). Without treatment, life expectancy is reduced. This places a great burden on healthcare systems due to the increased morbidity and mortality associated with the disease. Further, the economic impact of treating RA is significant, and health care costs limit the appropriate medical care of many patients in developing countries (2).

In Africa and South Africa (SA), similar to the rest of the developing world, the burden of communicable disease has overshadowed the focus on non-communicable diseases (NCD) including RA. This is despite mounting evidence that the prevalence of NCD is rising in sub-Saharan Africa, with the lower socioeconomic groups bearing the brunt of increasing NCD (3).

Both cross sectional and retrospective studies from Africa in recent years show RA is often severe and requires special attention (4-6). Despite this, little attention is given to rheumatic disease in Africa, with only a single rheumatologist providing care for the 16 million strong population of Kenya and thirty for the 40 million of South Africa as recently as 2003 (2).

There are limited studies from Africa and SA on the burden of NCD especially RA with only a single study from SA on the long term experience of RA. Tikly et al. showed that patients treated in a dedicated rheumatic unit had significant improvement in disease activity scores (5). In Tikly et al. study disease activity declined significantly from the first to the last visit and methotrexate was associated with improved survival time compared to other disease modifying anti-rheumatic drugs (DMARDs).

Similarly, our unit has been treating patients with rheumatoid arthritis for greater than 30 years however there is minimal data on the long term outcomes and management of these patients. There is a clear association with co-morbidities in RA and increased disease activity and joint damage. This study therefore seeks to understand the natural history of patients with rheumatoid arthritis treated in a tertiary/regional hospital.

The findings of this descriptive study will be relevant to clinicians working under similar circumstances in South Africa and other developing countries. They can potentially assist with policy implementation in the treatment of RA patients and will probably highlight challenges for better care and the need for expert rheumatologist services (7).

## **Aim**

To describe the demographic profile of patients with long standing established rheumatoid arthritis (greater than 10 years), attending a public sector arthritis clinic and their disease status and management.

## **Specific Objectives**

1. Describe the demographic profile of RA patients in a multi-ethnic public health care setting.
2. Describe the disease duration and document the proportion of sero-positive and sero-negative RA patients.
3. To document the number of patients with active disease after a minimum of 10 years and to determine if standard care of practice are followed
4. To describe disease activity in sero-positive and sero-negative RA patients.
5. Describe the co-morbid disease profile and describe if standard of care received is in keeping with a tertiary institution.
6. To document the use of disease modifying anti-rheumatic drugs in this cohort.

## **Keywords**

Rheumatoid arthritis, positive rheumatoid factor, comorbid disease, disease activity, disease modifying anti-rheumatic drugs, South Africa

## **Background and Literature**

### **Introduction**

Rheumatoid arthritis is a chronic inflammatory disease of unknown aetiology characterized by a symmetric, peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage, physical disability and premature mortality (1).

In addition, RA is associated with extra-articular manifestations including, but not limited to, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis and haematological abnormalities (1).

### **Pathogenesis of rheumatoid arthritis**

The pathogenic mechanisms of synovial inflammation in RA are driven by immune dysregulation, inflammation and a breakdown in self-tolerance. Multiple pathogenic mechanisms have been proposed, and a key pathway is the overproduction and over-expression of tumour necrosis factor (TNF), which results in both synovial inflammation and joint destruction (8, 9)

The causes of TNF overproduction include interaction between T and B lymphocytes, synovial-like fibroblasts and macrophages, leading to overproduction of several cytokines including interleukin-6 (IL6) which further drives persistent inflammation and leads to the clinical and laboratory manifestations of RA, as well as cartilage and bone damage, due to



chondrocyte and osteoclast activation (the latter primarily via the receptor activator of nuclear factor Kappa  $\beta$  ligand (RANKL–RANK system)) [Figure1](8, 10).

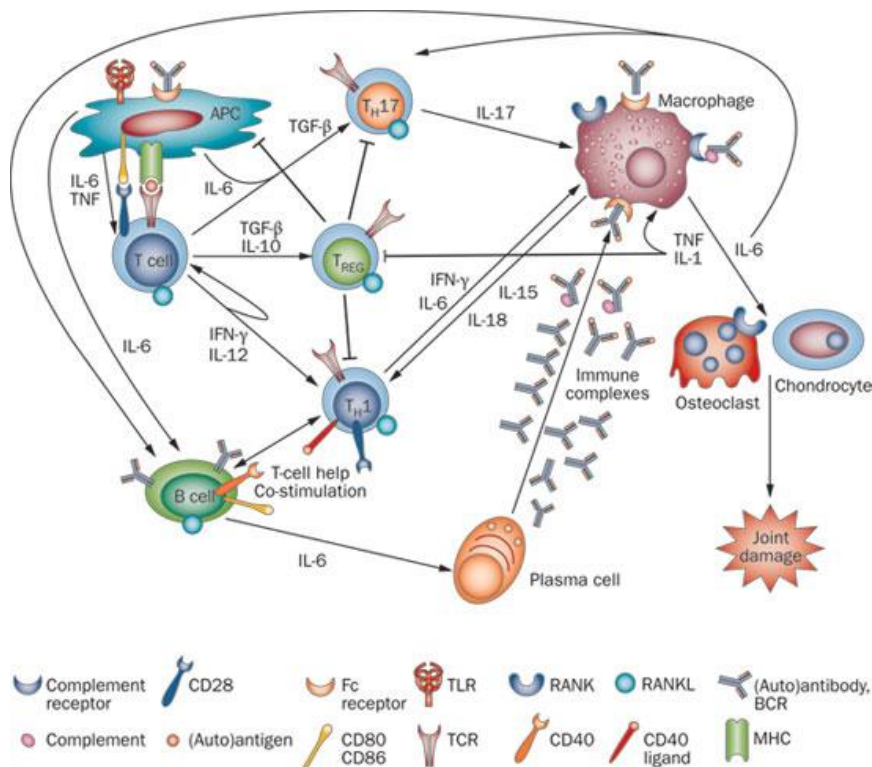


Figure 1. Pathogenesis of rheumatoid arthritis [10]

Rheumatoid arthritis synovium contains a predominantly T lymphocyte infiltrate, composed mainly of CD4<sup>+</sup> cells. The functional role of these T cells remains poorly understood and direct targeting of these T cells with cyclosporine or T cell depleting therapies showed limited or no efficacy. These findings suggest that specific T cell subsets may need to be targeted and attention has increasingly focused on the role of type 17 helper T cells (Th17) which induce macrophages to secrete proinflammatory cytokines and help B cells to produce (auto)antibodies that bind to target antigens forming immune complexes [Figure 1] (9, 10).

Apart from the accumulation of T cells, the rheumatoid synovium is also characterized by the infiltration of a variable number of B cells and antibody producing plasma cells supporting the theory that humoral adaptive immunity is integral to RA. The pathogenic role of CD20<sup>+</sup> B cells is confirmed by the efficacy of rituximab, a monoclonal antibody directed against CD20 in RA patients (10).

Additionally several other mechanisms have been implicated including the activation of the innate immune system, intracellular signalling pathways including the Janus kinase (JAK) pathways and mesenchymal tissue response which all contribute to the complex interplay of inflammation in RA and continue to be investigated in search for newer more effective therapeutic agents (1, 10).

### **Autoantibodies in rheumatoid arthritis**

Rheumatoid factor autoantibodies are found in 75-80% of RA patients at some time during the course of the disease. Immunoglobulin M (IgM) and immunoglobulin A (IgA) rheumatoid factors are key pathogenic markers directed against the Fc fragment of immunoglobulin (IgG). High titre of IgM RF are relatively specific for the diagnosis of RA in the setting of a chronic inflammatory polyarthritis and were for decades the only serological criterion widely used in the diagnosis of RA (1).

More recently identified and increasingly important antibodies, are those directed against citrullinated peptides. Anti-cyclic citrullinated peptide (CCP) antibodies are produced in the liver and are directed against deaminated peptides. These antibodies recognize citrulline-containing regions of several different matrix proteins including filaggrin, keratin, fibrinogen and vimentin and are found in higher concentrations in the joint fluid than in the serum (1, 11).

The majority of patients with anti-citrullinated protein antibody (ACPA) positive disease are also positive for RF, however anti-CCP antibodies have a higher specificity for RA. The sensitivity of ACPA assays for RA varies from about 50 to 75%, depending upon the assay and study population, while specificity of ACPA is relatively high, usually over 90%. Positive ACPA testing also appears to predict an increased risk for progressive joint damage and radiographic progression more effectively than RF (11-13)

### **Genetic Factors**

A clear relationship exists between genetic factors and RA with at least a 50% risk of developing RA being attributable to genetic factors. There are more than 30 genetic regions associated with RA, the major identified areas are PTPN22 and human leucocyte antigen (HLA) genes (14, 15).

Genetic studies of the HLA-DR alleles found that the DR4 allele was the most common association among South African patients. Mody et al. found that the frequency of DR4 was 44% in Blacks of Zulu descent in Durban with RA compared to 10% in matched control subjects (16). Similarly studies from Cape Town in Whites, Blacks and patients of Mixed Ancestry also showed a consistent association of HLA – DR4 in all population groups with a relative risk of 3,2 in Whites, 3,9 in Blacks and 3,7 in patients of Mixed Ancestry with RA (17).

The HLA alleles share a common motive, which is known as the shared epitope and recent genetic studies show differences in ACPA status of patients with RA, which relate to the number of specific HLA-DRB1 alleles (14, 15).

### **Environmental Factors**

Several environmental risk factors are thought to increase the risk of RA and the best studied amongst them is smoking. Smoking doubles the risk of developing RA especially in ACPA-positive patients who are positive for HLA-DRB1 shared epitope alleles (18).

Other potential environmental risk factors are alcohol, coffee, vitamin D status, oral contraceptive use and a low socioeconomic status (19).

### Epidemiology of rheumatoid arthritis

There is a wide geographically and ethnic variation in the prevalence of RA within countries. The native American Pima Indians of North America have one of the highest prevalence rates (7%) while other population studies from Africa and Asia show lower prevalence rates in the range of 0.2-0.4% [Figure 2] (1).

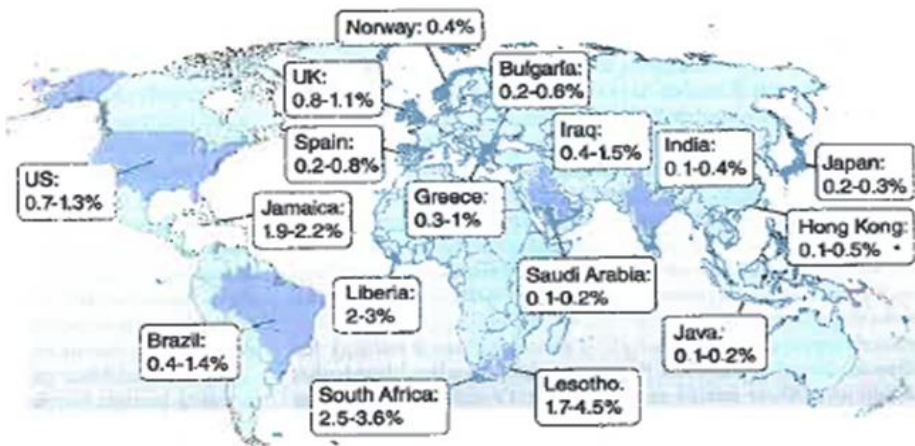


Figure 2. Prevalence rates of rheumatoid arthritis [7]

Rheumatoid arthritis affects approximately 0.5-1% of adults in the developed world. The disease is three times more common in women than men with prevalence increasing with age in both sexes. The highest prevalence is seen in women aged 65 years and over, suggesting a possible role for hormonal factors (1).

There are limited studies on RA from Africa and these have been concentrated in a few countries (SA, Nigeria and Uganda) with no reported data from the rest of Africa (4).

Although traditionally RA was thought to be rare in Africa and with a milder disease course, compared to the developed world, recent studies suggest an increasing incidence of RA. The first systematic literature review of the burden of RA in Africa by Dowman et al. (2011), showed a prevalence of 0.36% in 1990 which translates to a burden of 2.3 million affected individuals in 1990. Projections for 2010 based on the same prevalence rates would suggest a crude prevalence of 0.42% and the burden increased to 4.3 million people in Africa. This figure is thought to be an underestimation of the true burden of RA as it has been noted that hospital based studies under-report the prevalence by about 6 times in comparison to population based studies (4).

The exact incidence of RA in Africa presently remains uncertain but there is mounting evidence showing that the frequency of RA is increasing in the indigenous populations of

East, Central and South Africa, although it remains rare in West Africans (20). The few studies from SA show higher disease activity and prevalence in mixed urban community in Soweto (0.9%), compared to rural areas where both disease activity and prevalence is lower (Tswana of West Transvaal (0.1%), the Xhosa of Transkei (0.68%) and the Sotho's in Lesotho (0.3%) Venda (0%)) (21-23). The reasons for the lower rates of RA in rural African populations remains unclear but the distinct urban rural gradient strongly supports environmental factors as an important causative role in the pathogenesis of RA.

Although the mean age of onset of RA at 36.6 years in Blacks is significantly lower than the 44.2 years in Caucasians (24) there is no gender difference and in both groups there is a greater female preponderance of RA, similar to international reports (1). Genetic studies of the HLA DR alleles show that DR4 is the most common association and has been noted in patients of Zulu, Xhosa and Sotho descent in multi-center studies (1, 16, 17).

### **Clinical manifestations and systemic consequences of rheumatoid arthritis**

Rheumatoid arthritis causes inflammation of the joints, tendons and bursae and subjects present with pain, swelling and early morning joint stiffness usually lasting more than one hour duration. The earliest affected joints are typically the small joints of the hands and feet and the initial pattern of joint involvement may be mono-articular, oligoarticular or polyarticular and usually in a symmetric distribution (1).

Extraarticular manifestations may develop during the clinical course of RA or even prior to the onset of arthritis. Predictors for extra-articular disease are smoking, sero-positive RF disease and early onset of severe physical disability (25). The most frequently observed extraarticular manifestations worldwide are subcutaneous nodule, secondary Sjogren's syndrome, pulmonary nodules and anaemia (1). The only study from SA, on the extra-articular RA manifestations in African patients found a similar frequency and spectrum to the published literature (24, 26).

### **Diagnostic Imaging**

Untreated RA is an aggressive disease and leads to bone erosions in 80% of patients within one year of diagnosis (10). Juxta-articular erosions are usually irreversible and characterize uncontrolled inflammation and are used as a measure disease activity. They are identified readily on hands and feet plain radiography. Two typical erosions are sufficient to confirm a diagnosis. Extensive ongoing damage on radiographs suggests inadequately controlled RA (8).

Radiographs serve as a useful baseline for evaluating disease activity during treatment and should be repeated every two years in patients with remission or with low disease activity. Therapy is considered insufficient if there is radiological evidence of disease progression (25).

There is irrefutable evidence that DMARD's when used early in the course of the disease, slow radiographic progression and reduce long term disability.

Although conventional radiography was the diagnostic modality in RA, recently there has been extensive interest in new imaging modalities, particularly ultrasound (US) and magnetic resonance imaging (MRI) which can assess both reversible and irreversible structural changes (8)

The advantages of the newer imaging techniques are a greater sensitivity in detecting synovitis, joint space narrowing and erosions earlier than conventional radiographs and the ability to provide unique additional information on disease activity (27).

Ultrasound Doppler has useful negative predictive value in patients with high pre-test probabilities of development of RA (8). On a therapeutic front, precise visualisation of anatomical structures with bedside ultrasound facilitates allows for accurate placement of intra-articular injections, however, these are not yet part of routine patient management (7). The inter-observer variability and poor acoustic window, such as mid-carpus has to some extent restricted the value of US in routine practice despite widespread use in academic and research fields (8, 27).

In contrast, MRI allows a three-dimensional perspective and precise assessment of the bony and soft tissue structures within a targeted joint. The main 'activity' findings detected by MRI include synovitis, tenosynovitis and bone marrow oedema (BME) while the 'damage' findings include bone erosions and joint space narrowing. The major limitation is that MRI criteria for diagnosis of RA are not uniformly defined, and the scoring system requires further detail, perhaps best decided by well-designed studies in this area (27).

Tamai et al. reported a scoring system using baseline ACPA and/or RF, MRI findings of symmetrical synovitis and MRI BME and/or bone erosion which could predict early RA with 82.5% sensitivity and 84.8% specificity (28).

### **.Diagnostic Criteria**

As the understanding of the pathogenic mechanisms of RA have improved, this has led to the availability of new therapeutic drugs that have enhanced the management of RA. Moreover, it has been recognized that early therapeutic intervention improves clinical outcomes and reduces the accrual of joint damage and disability (29).

These developments resulted in the American College of Rheumatology (ACR) revising the diagnostic classification criteria with the goal of identifying patients who would benefit from early effective intervention (29). The previous ACR1987 criteria were limited in identifying individuals with very early RA.

In 2010, the ACR and the European League Against Rheumatism (EULAR) developed new classification criteria for RA, with the objective of improving sensitivity in detecting early disease (29).

The new classification system redefines the current paradigm of RA by focusing on early features of disease that are associated with persistent and/or erosive disease and not the late

stage features of erosive joint damage and extra-articular disease changes that can now be prevented with newer agents (8).

The criteria assess joint involvement, autoantibody presence, acute phase response levels and symptom duration (Table 1)

**Table 1. ACR/EULAR 2010 Rheumatoid Arthritis Classification Criteria [8]**

		Score
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, thumb IP, MTP, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive anti-CCP antibodies ( $\leq 3$ times ULN)	2
	High-positive RF or high-positive anti-CCP antibodies ( $> 3$ times ULN)	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	$\geq 6$ weeks	1

**Note:** These criteria are aimed at classification of newly presenting patients who have at least one joint with definite clinical synovitis that is not better explained by another disease. A score of  $\geq 6$  fulfills requirements for definite RA.

**Abbreviations:** ACPA, anti-citrullinated peptide antibodies; CCP, cyclic citrullinated peptides; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IP, interphalangeal joint; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RF, rheumatoid factor; ULN, upper limit of normal.

**Source:** D Aletaha et al: *Arthritis Rheum* 62:2569, 2010.

Serum autoantibodies such as RF and ACPA are used as biomarkers for both diagnostic and prognostic significance and can precede the clinical manifestation of RA by many years (1). A small proportion of patients eventually diagnosed with RA may be positive for RF, but not for ACPA in the early stages of their presentation; thus measurement of both RF and ACPA, rather than ACPA alone, improves the specificity and sensitivity of serological testing for establishing a diagnosis of RA (12).

Importantly prognosis varies within sero-positive and sero-negative disease respectively. Clinical studies demonstrate that RF and ACPA positive disease are different from autoantibody negative disease. The synovium of patients with ACPA positive disease have more lymphocytes compared with ACPA negative who have more fibrosis and increased thickness of the synovial layer (30).

Moreover, higher titres of RF are found to correlate with extra-articular manifestations such as interstitial lung disease and vasculitis compared to RF negative disease. Although RF titres may fall with effective treatment of RA in patients who are originally RF-positive, this is not used as a measure of disease activity (12).

## **Disease Activity Assessment**

The success of therapy for RA relies on the goals of treatment to be specified in advance and to fulfil the response criteria that categorize improvement into either good or moderate response. The EULAR response criteria are based on the Disease Activity Score 28 (DAS 28) and thus measuring disease activity is an integral part of the management of RA (31).

Common indicators of disease activity in RA include:

- Pain
- Swollen and tender joint counts
- Patient and evaluator global assessment of disease activity
- Erythrocyte sedimentation rate (ESR) and C-Reactive protein (CRP)
- Duration of morning stiffness
- Fatigue
- Functional activity scales

There are several methods of scoring disease activity in RA, where the clinical examination of tender and swollen joints, global assessments and laboratory investigations are combined in a composite disease activity score. The 3 validated scores currently in use in SA are the DAS-28, the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) (7).

These scores allow classification into a state of remission, low, moderate or high disease activity and provides a simple tool for assessing disease at each patient visit to guide therapeutic decisions (7). The SDAI and CDAI were validated in their original studies in addition to several cross sectional cohorts. The Pearson correlation analysis between DAS28, SDAI and CDAI showed an excellent correlation between these scores and patients' disease activity (31, 32).

As active RA causes a substantial effect on physical functioning, instruments designed to measure physical function are useful indicators of disease activity. The complete Health Assessment Questionnaire (HAQ) is a comprehensive tool designed to assess patient disability, discomfort, medication, side effects, cost and mortality. Of these components only the HAQ Disability Index (HAQ-DI) is used frequently in clinical trials and clinical practice. It evaluates patients' ability to perform activities of daily living through their self-reported answers to 20 questions designed to assess upper or lower extremity use (31).

Finally while there are limitations inherent in the use of global ordinal scales, the ACR 1991 global functional status in RA is a useful and accepted score to describe the global functional consequences of RA especially with regard to work disability (33).

## **Acute phase response in rheumatoid arthritis**

The main clinically useful biologic markers in patients with RA include acute phase reactants (APR), particularly the ESR and the CRP. The APR describes the local and systemic inflammatory and repair processes that accompany inflammation.

The ESR level tends to correlate with disease activity in RA as well as disease severity and may be useful for monitoring therapeutic response (34). The use of ESR is limited by the size, shape and number of red cells as well as other plasma constituents such as immunoglobulins.

The CRP is a more objective measure of disease activity in RA, however elevations of both CRP and ESR are stronger indications of radiological progression than CRP alone (35). In a study of 147 patients by Heijde et al, absence of progression of radiographic joint damage after two years was correctly predicted in 83% of the patients using a combination of disease activity at presentation (assessed by ESR, CRP, or disease activity score) and DR4 and RF positivity (36).

In contrast Yildirim et al., reported an association between APR and DAS28, and showed the CRP was the most useful biochemical marker for evaluating the disease activity of patients with RA (37).

Interestingly, these markers of systemic inflammation also confer a statistically significant increased risk for cardiovascular death among patients with RA, even after controlling for additional cardiovascular risk factors and comorbidities (25). Further, observational studies show an increased risk of cardiovascular disease (CVD), which correlates with the activity and duration of the RA measured by these APR's (38).

Other markers used include a low serum haemoglobin and low serum albumin in association with increased disease activity (39). A recent finding suggests that RA patients with anaemia have more severe disease. Mody et al. (1989) reported anaemia as the most common extra-articular manifestation of RA in Black South Africans (26). It is postulated that the anaemia is mediated by inflammatory cytokines, in particular interleukin (IL6) (39, 40). Similarly, a reactive thrombocytosis associated with active RA is most likely due to the pro-inflammatory effects of interleukin1 $\beta$  and interleukin 4 (41).

### **Rheumatoid arthritis and associated co-morbid diseases**

Rheumatoid arthritis is associated with an increased prevalence of other NCD. On average, the established RA patient has two or more comorbid conditions and these play a pivotal role in RA management and outcomes. It has been shown that the higher the number of comorbid illnesses, the higher the medical costs, disability and the risk of mortality. This is emphasized by Michaud and Wolfe in their seminal report on comorbidities in rheumatoid arthritis "It should be the responsibility of the rheumatologist to take this and the risk of additional conditions into account when treating the patient" (42).

The NCD associated with RA are cardiovascular disease (CVD), infections, lymphoproliferative malignancy, gastrointestinal disease and osteoporosis (43).

A small study by Bishri et al, of 340 patients with RA found that the most common comorbidities were hypertension (35.9%), diabetes (30.9%) osteoporosis (25.8%) and dyslipidaemia (19.4%) (44). Not surprisingly, it is now well established that CVD is the leading cause of death in patients with RA (45).



## **Rheumatoid arthritis and cardiovascular disease**

Accumulating evidence suggests that atherosclerosis and CVD are truly inflammatory disorders sharing a common pathophysiology with the synovial inflammation and pannus formation that characterize RA. Indeed it has been suggested that atherosclerosis and CVD be considered “extra-articular manifestations” of RA. Overlapping pathogenic features of the two diseases include the predominant role of pro-inflammatory cytokines (e.g. TNF alpha and IL-6) elevated serum levels of APR (including CRP, fibrinogen and serum amyloid), abnormal endothelial function and neoangiogenesis. The unchecked cellular dysregulation is postulated to account for the increased prevalence and severity of coronary calcification in RA (43, 46)

In many ways, CVD in RA shares similarities with CVD in diabetes mellitus (DM). Preclinical atherosclerosis and the risk of CVD appears to be of equal frequency and severity in RA and DM of similar duration (46) and RA is associated with increased rates of cardiovascular illness, including myocardial infarction, cerebrovascular events and cardiac failure.

Further, the medications used to treat RA might have dual effects on risk for cardiovascular (CV) morbidity. This is exemplified by the use of corticosteroids which may decrease CV complications in RA by decreasing inflammation but also increase CVD by promoting pro-atherosclerotic lipid profiles, hypertension and insulin resistance (46).

Therefore, it is now widely accepted that atherosclerosis in RA is associated with both traditional CV risk factors such as age and hypertension, as well as non-traditional risk factors of ongoing inflammation as in RA (47).

## **Infection in rheumatoid arthritis and treatment associated comorbidity**

The increased rate of infection in RA is well documented when compared with a healthy control population. The increased risk is seen for all types of infections and for infections requiring hospital admission (43, 48).

The risk is increased in patients with higher disease activity scores, and multiple comorbidities (diabetes, alcoholism, chronic lung disease) and the use of corticosteroids (48).

The use of immunosuppressive agents which may impair immune function further increase the risk of serious infections, however McLean-Tooke et al, in a systematic review of the literature, reported minimal if any, increased infection risk in patients on low dose methotrexate (MTX) (48).

In contrast, a meta-analysis of the risk of serious infection in patients on biological treatment found that standard dose and high dose biological drugs (with or without traditional DMARD's) but not low dose biological drugs, were associated with an increased risk of serious infections in RA patients compared to use of traditional DMARD's only (49).

This is of particular interest in SA, where the increased use of biological drugs especially TNF alpha inhibitors pose a serious risk for development of tuberculosis (TB) infection due to the high burden of the TB endemic in sub-Saharan Africa and the essential role TNF plays in the containment of mycobacterial infection. Several studies have confirmed the relationship between use of infliximab (TNF inhibitor) and TB infection and the guidelines recommend that physicians should screen patients for latent TB infection or active disease prior to starting any biological treatment (50).

The current recommendation is that TNF inhibitors as well as other biological agents should not be used in RA patients with ongoing active infection and should be used with caution in those with high risk of infection (i.e. diabetes mellitus, splenectomised patients) (43).

In the South African context the high incidence and prevalence of human immunodeficiency virus (HIV) infection poses several challenges to the treatment of RA patients and information on the safety of using immunosuppressive drugs in an HIV infected patient is limited. Methotrexate and biologic drugs place patients at risk of opportunistic infections and there is concern about the effects of immunosuppression in an HIV-infected patient not on anti-retroviral therapy. It is therefore recommended in patients not on anti-retroviral therapy or who are virologically suppressed that hydroxychloroquine (HCQ) (which may have antiviral properties) or sulphasalazine (SSZ) may be more appropriate choices (7).

### **Rheumatoid Arthritis Treatment**

The aim of treatment in RA is the minimisation of disease activity using a combination of DMARDs and biological agents, with or without glucocorticoids according to the disease activity status. Achieving and maintaining low disease activity using a single or combination DMARDs as quickly as possible improves long term outcomes and is cost-effective compared with older, more gradual approaches to initiating DMARD therapy (1, 8)

Disease modifying anti-rheumatic drugs are named because of their ability to slow or prevent structural progression of RA and were introduced in the 1970's and early 1980's. The most commonly used DMARD's in the past were gold, penicillamine and minocycline all of which produced a slow response with an associated high level of toxicity, resulting in low compliance rates and due to their varying degrees of success and inconsistent clinical efficacy are no longer used (1, 7, 25)

Later, drugs included HCQ and SSZ, both used for early mild disease or as adjunctive treatment (1). Although hydroxychloroquine has not been shown to delay radiographic progression of RA and is thus not considered to be a true DMARD, in contrast SSZ has been shown in randomized controlled trials to reduce radiographic progression of the disease (1).

The introduction of MTX and its widespread use in the late 1980's dramatically changed the therapeutic landscape of RA. Methotrexate was approved for the treatment of RA in 1986 and remains the drug of choice and the benchmark for testing efficacy and safety of all new disease modifying therapies.

Methotrexate is administered as long term therapy, usually in a range between 7.5 to 25mg weekly. The maximum therapeutic doses of MTX used in rheumatology practice has increased in recent years (8). Several studies show long term compliance and remission on MTX (51, 52). Choi et al. showed a 60% overall reduction in mortality in subjects on MTX (53).

A systematic literature review on the long term safety of MTX monotherapy in patients with RA demonstrated good tolerability of the drug and favourable long term safety (54, 55). Data on MTX use and compliance show that approximately 60% of patients receiving high dose MTX (12.5mg/week) are still using the drug after 6 years and in a separate twelve year follow-up of 460 patients treated with MTX, 53% of patients were continuing to take MTX at 12 years (irrespective of any periods of temporary discontinuation) (54).

Methotrexate does, however, have several adverse effects with varying severity. The risk of MTX side effects is influenced by the dose and treatment regimen. Adverse effects of MTX include those that are minor (e.g. nausea) and those that are serious (e.g., hepatotoxicity, blood dyscrasias and interstitial lung disease). Monitoring of adverse effects includes, pre-treatment screening and subsequent safety recording of blood counts and liver function tests should continue throughout the course of therapy (1).

When MTX is contraindicated, sulfasalazine or leflunomide are alternatives (1). Disease modifying anti-rheumatic drugs are sometimes combined and several combinations of DMARD's have proven efficacy (51, 52). An example is methotrexate, sulfasalazine and hydroxychloroquine – termed triple therapy. A randomised trial comparing combination therapy with single drug therapy MTX in early RA demonstrated that combination therapy was better and not more hazardous than single treatment in induction of remission in early RA (51).

### **Biological Agents**

With the improved understanding of the pathogenesis of RA, biological DMARDs that are intravenous protein therapeutics targeting cytokines and cell surface molecules have been developed. These may be classified into TNF inhibitors and non-anti-TNF agents and these include, but are not limited to, B cell targeted therapy against CD20 such as rituximab, T cell co-stimulation blockade with the fusion protein abatacept and interleukin-6 receptor inhibition with tocilizumab (1, 8).

The use of biological agents together with MTX has made clinical remission and radiographic non-progression a realistic and achievable goal in patients with early and severe RA (56). Investigators in the Early Rheumatoid Arthritis (ERA) trial comparing etanercept to methotrexate monotherapy showed a better ACR20 response in the etanercept group than that for MTX at 24 months (72% vs 59%, respectively,  $p=0.005$ ) (57).

Further, the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study showed that the combination of etanercept and MTX was significantly better in reducing disease activity, improving functional disability and retarding radiographic

progression compared with MTX or etanercept alone (56). This highlights the pivotal role of methotrexate plays in RA therapy.

In SA, the guidelines for use of biological therapy recommend a six month trial of at least three synthetic DMARDs (including MTX, unless contraindicated) before commencing biological agents. This seems reasonable, given resource constraints, and given that up to one third of all patients will achieve low disease activity on synthetic DMARD therapy (58, 59). Additionally, due to significant cost implications biological agents are limited in both the South African public and private health sector (7).

### **Surgical Treatment**

Surgery in RA is reserved for severely damaged joints and while total joint replacements or arthroplasties may be done on any joint, the most successful procedures are carried out on hips, knees and shoulders. The goals of such surgery are to reduce disability, pain relief and improve quality of life (1).

Although surgical treatment is widely available, there are significant delays in the public health care sector in SA due to costs and resource constraints. A multi-ethnic single entry survey of 256 RA patients in a specialized rheumatology and orthopaedic hospital in 1988, in Cape Town found that 49.2% of patients had at least one surgical procedure and that 15.6% had a replacement arthroplasty of one or more of the four major weight bearing joints (60).

Fortunately due to better drug treatment, the need for joint surgery has decreased and a study from Ireland, showed the total number of hip and knee joint arthroplasties in patients with RA decreased from 1995 to 2010, despite substantial increases in those procedures among the general population (61).

### **Expert Care**

There is convincing evidence that an expert in the treatment of rheumatic diseases, such as a rheumatologist, should participate in the care of patients with inflammatory arthritis who are suspected of having RA and the ongoing care of patients diagnosed with this condition. The initial and continued care of patients with RA by a rheumatologist is associated with better disease outcomes compared with care rendered primarily by other clinicians (2, 7, 62).

### **Long term rheumatoid arthritis – prognosis, functional and social outcomes**

Rheumatoid arthritis is recognized as a disease with a natural history of severe long term outcomes (63, 64) and is associated with reduced life expectancy of a median of 10 years in men and 11 years in women (45). Significant predictors of poor function include functional status, female gender and disease activity state at disease onset (65).

Rheumatoid arthritis has a significant impact on health-related quality of life, and is associated with increased mortality and health care costs when compared to the general population. Many of the patients are unable to work and thus become dependent on the state

for their health services and social welfare support, resulting in psychological problems and an increasing economic burden for the country.

However, with early successful treatment the patients can return to the workforce decreasing the burden on the state, resulting in a substantial reduction in the costs to society (42).

The social aspects of living in RA have been studied in Soweto, SA and the following observation was made “The experience of living with RA in a low resource context are similar to those in a mid and high resource contexts, but are exacerbated by poverty and lack of basic services. Pain and social exclusion are some of the key experiences of women with RA living in Soweto” (66).

Importantly, low levels of formal education and poor socioeconomic status have been identified as risk factors for poorer outcome in RA (67).

### **South African Perspective**

Contemporary epidemiological data on the prevalence and incidence of RA in South Africa are limited to only a few studies (4, 20).

There is only one recent study on the long term outcomes by Solomon et al, in established RA, and the study found a need for tighter RA control in the South African public health care sector, where results of disease outcome measurements were poorer in public care patients than in private care patients. This highlights the need for better disease activity control of RA in the public health care sector in South Africa and regular audits of patients (6).

## **Methodology**

### **Study design**

This is a retrospective, descriptive chart review of established RA patients attending a tertiary arthritis public health sector clinic for a period greater than 10 years.

### **Study Population**

Kwazulu Natal (KZN) has a multi-ethnic population which is unique because of its large Indian population (originally from the Indian sub-continent). According to Census South Africa (2011), KZN has a population of 10.2 million people, about 85% of whom are Black Africans followed by 9.5% Indian (68).

King Edward VIII hospital was established in 1936 for a mainly Black South African population because of racial segregation under the previous apartheid government and therefore the population serviced a mainly indigent Black/ Indian group of South Africans.

The arthritis clinic was established in the early 1970's, as a specialist based clinic, affiliated to the Department of Internal Medicine, University of Natal. Initially managed by physicians with an interest in rheumatology it became a rheumatologist based clinic in the early 1980's.

In 2003, a central tertiary hospital was opened and the rheumatology department along with other sub-specialties relocated to the new centre. The arthritis clinic continued to function in King Edward hospital but under the primary care of medical officers with an interest in rheumatology. There was no continuation of specialist rheumatologist care or specialist physician service for the clinic during this time. Therefore the majority of patients with active disease were transferred in 2003 and those patients who remained at the clinic were those who were unwilling to transfer or who were deemed to have early mild disease or disease remission.

In April 2015 the clinic became a specialist based clinic, run by a rheumatologist and physicians with an interest in rheumatology and all files have been subsequently re-revised and patient management reviewed.

### **Sampling strategy**

A carbonated copy of all file are kept for every patient in the clinic and all RA patient files will be reviewed. All files with RA with >10 years from diagnosis, with patients in current attendance, will be reviewed for the study purpose.

### **Sample size**

All files of patients attending the clinic for greater than 10 years will be reviewed.

### **Inclusion criteria**

All patients with established rheumatoid arthritis as defined by the clinical notes and by that fulfilled the 1987 ACR criteria.

### **Exclusion criteria**

Patients with RA for less than 10 years duration.

Patients who are no longer in attendance at the clinic.

Patients with a diagnosis of psoriatic arthritis and/or overlap syndromes or

Patients diagnosed with autoimmune disease.

### **Data collection methods and tools**

The clinic files for all patients who meet inclusion criteria will be assessed and data extrapolated using a standardized data collection tool sheet.

- The following data will be collected: clinical notes, radiological reports and laboratory results.
- All data will be directly entered onto the data collection sheet by the principal investigator.
- The data will be checked to ensure reliability and validity and to minimize error.
- Sample bias will be eliminated as all patient files that meet inclusion criteria will be documented.

The following data will be collected from patient files:

## Demographic

1. Age
2. Gender
3. Ethnicity – will be documented as Black/Indian/Mixed Ancestry/Caucasian
4. Date of diagnosis – the earliest recorded date of RA diagnosis or symptom onset will be considered the incidence date of disease.

## Clinical

1. Number of tender and swollen joints
  - The number of tender and swollen joints noted at the most recent visit will be scored according to the SDAI and captured.
2. Duration of early morning stiffness, at most recent visit, will be recorded.
3. Modified functional class
  - This will be defined by the ACR 1991 revised criteria for the classification of global functional status in RA.
4. Document the co-existent comorbid disease/s and the duration – at enrolment and at >10 years
  - Diabetes mellitus was recorded as present if there was a clearly documented history of diabetes and/or current treatment with hypoglycaemic agents.
  - Hypertension was recorded as present if there was a physician's diagnosis of hypertension in the medical records and/or were receiving antihypertensive agents.
  - HIV was recorded present if there was a positive test result in the patient file and/or the patient receiving highly active anti-retroviral therapy.
  - Dyslipidaemia was defined according to the cut off values as recommended by the South African dyslipidaemia guidelines and or statin therapy
  - Osteoporosis was defined according to bone mineral density results and or treatment with bisphosphonates
  - Other : any other disease will be specified and duration
5. Document the treatment
  - Use of DMARD therapy will be documented
    - Drug name
    - Duration
    - Reason for discontinuation
  - For each individual drug, as recorded in clinical notes will be recorded

## Investigations

The following results as per last visit will be recorded:

1. Haemoglobin
  - Hb < 12g/dL in females and Hb <13g/dL in males
2. CRP
  - A value greater than 16mg/dL will be considered elevated

## 3. ESR

- Sustained elevation of the ESR was defined as >2 recorded ESR values of >60mm/hr. with a minimum interval of 30 days between two measurements.

## 4. RF

- Rheumatoid factor will be documented as positive as documented by clinical notes and/or laboratory reports in patient's files.

## 5. ACPA

- Anti citrullinated protein antibody test will be recorded as either present or absent.

## Imaging

Radiographs done at initial assessment and reported on by a radiologist will be recorded as either present or absent in the following fields:

- Erosions
- Joint space narrowing
- Juxta-articular osteopenia

## Osteoporosis

The World Health Organization (WHO) Classification of osteoporosis was used for patients who had bone mineral densitometry scans done (69).

The WHO criteria for the diagnosis of osteoporosis is shown in Table 2.

Table 2. WHO Classification of Osteoporosis (69)

Normal bone	T-score better than -1
Osteopenia	T-score between -1 and -2
Osteoporosis	T-score less than -2.5
Established osteoporosis	Presence of a non-traumatic fracture

**Data management**

- Each file will be assigned a unique study number.
- Data will be de-identified and captured onto an Excel spread-sheet and will be password protected.
- Only the investigators will have access to the master copies. Only de-identified data will be submitted for analysis.

**Statistical analysis**

Data will be extracted to answer the objectives of the study. A statistician will assist with analysis.



- Descriptive statistics and frequency tables will be used to report the demographic characteristics (age, gender and ethnicity) of the study population.
- Cross tabulations and student t-tests will be used to determine age, gender and ethnicity specific differences.
- Chi square will be used for categorical variables.
- The significance of the test will be set at  $p < 0.005$

### **Study location**

King Edward VIII Hospital is located in Durban, KZN. It is the second largest hospital in the southern hemisphere providing regional and tertiary services to the whole of KZN and parts of the Eastern Cape. King Edward is a 922 bedded hospital with approximately 360 000 out – patients (70).

It is a teaching hospital for the University of KwaZulu Natal (UKZN), Nelson R Mandela School of Medicine and has a nursing college attached to it with a full range of medical and surgical specialties (70).

### **Study period**

This is a retrospective chart review of 2016. The patient files reviewed will cover a period from 1990-2016.

### **Limitations to the study**

There are several limitations to the present study, many relating to its retrospective nature.

These include absent or missing data, absence of a comparator group and lack of standard use of composite disease activity scores and ACR response criteria, now widely used in clinical trials, to indicate disease activity and remission.

Inter-observer variability, as evaluations of patients were made by several clinicians over time, may result in poorly representative data, as does the lack of validated tools for measurement of disease activity.

It was also not possible to assess the impact of the disease on employment status since this was, in most cases, only recorded at presentation and not on an on-going basis. Functional outcome has been used as a surrogate.

Analysis of mortality was not possible as such data would not have been captured in the clinic files and those files that are not available. Further adherence rates cannot be calculated as no registry exists.

The patient population in our clinic is biased with regard to ethnicity and race due to the country's apartheid legacy as discussed above and will be pertinent to Indian and African population only. Furthermore, due to the transfer of the department of rheumatology to a central hospital in 2003, a significant proportion of patients were moved, resulting in a skewed patient profile as patients requiring expert care were transferred across at this time.

Finally, the patient in this clinic may represent patients with less aggressive disease and fewer extra-articular manifestations and therefore outcomes and use of DMARDS may differ compared to patients with more aggressive disease. Despite this there is such a paucity of data from SA on RA and this audit may still provide extremely valuable information in our setting.

### **Timeline**

Submission of protocol to postgraduate office and for ethics approval – March 2016

Collection of data – July to August 2016

Analysis of data – September 2016

Write up of findings – October to November 2016

### **Ethical considerations**

#### **Scientific Validity**

No audit of this nature has been done in this clinic before. This study is valid as it will provide relevant knowledge on the patient population, management and care of patients attending the King Edward VIII arthritis clinic.

#### **Confidentiality**

This is a retrospective chart review study. There will be no patient contact. Patients will be captured on the data collection tool using only their initials and study identity number.

#### **Informed Consent**

Informed consent was not obtained for the study as it is a retrospective chart review. Ethical approval will be obtained from the Biomedical Research ethical committee of UKZN and gatekeeper permission to obtain records will be obtained from King Edward VIII hospital and Department of Health.

#### **Conflict of Interest**

There is no conflict of interest.

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## **Appendix 2: Ethical approval (BREC)**



17 August 2016

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Protocol: A retrospective review of the demographic profile, disease activity, co-existent co-morbid disease and treatment in established rheumatoid arthritis at a tertiary centre clinic.

Degree: MMed

BREC reference number: BE222/16

#### EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 23 March 2016.

The study was provisionally approved pending appropriate responses to queries raised. Your response dated 21 July 2016 to queries raised on 26 April 2016 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 17 August 2016.

This approval is valid for one year from **17 August 2016**. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **13 September 2016**.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely,

Professor J Tsoka-Gwegweni  
Chair: Biomedical Research Ethics Committee

cc supervisor: [paruk@ukzn.ac.za](mailto:paruk@ukzn.ac.za)  
cc Postgrad: [konar@ukzn.ac.za](mailto:konar@ukzn.ac.za)

**Biomedical Research Ethics Committee**

**Professor J Tsoka-Gwegweni (Chair)**

**Westville Campus, Govan Mbeki Building**

**Postal Address: Private Bag X54001, Durban 4000**

**Telephone: +27 (0) 31 260 2486 Facsimile: +27 (0) 31 260 4609 Email: [brec@ukzn.ac.za](mailto:brec@ukzn.ac.za)**

**Website: <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>**



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## **Appendix 3: Department of Health Provincial Approval**



**health**

Department:  
Health  
PROVINCE OF KWAZULU-NATAL

**DIRECTORATE:**

Physical Address: 330 Langalibalele Street, Pietermaritzburg  
Postal Address: Private Bag X9051  
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782  
Email: [hrkm@kznhealth.gov.za](mailto:hrkm@kznhealth.gov.za)  
[www.kznhealth.gov.za](http://www.kznhealth.gov.za)

**Health Research & Knowledge  
Management**

HRKM Ref: 147/16  
NHRD Ref: KZ\_2015RP0\_954

Date: 27 May 2016  
Dear Dr A. Singh  
Email: [akirakatie.singh@gmail.com](mailto:akirakatie.singh@gmail.com)

### Approval of research

1. The research proposal titled 'A retrospective review of the demographic profile, co-existent co-morbid diseases, disease activity and treatment in a cohort of established rheumatoid arthritis patients at a tertiary centre clinic' was reviewed by the KwaZulu-Natal Department of Health.

The proposal is hereby **approved** for research to be undertaken at King Edward VIII Hospital.

2. You are requested to take note of the following:
  - a. Make the necessary arrangement with the identified facility before commencing with your research project.
  - b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.
3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to [hrkm@kznhealth.gov.za](mailto:hrkm@kznhealth.gov.za)

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

**Dr E Lutge**

Chairperson, Health Research Committee

Date: 31/07/16

## **Appendix 4: Data Collection Tool**

**DATA COLLECTION SHEET**

Study Number:				
Male	Female	Date of Birth:		Age:
Black	Indian	Mixed Ancestry	White	
Urban	Rural	Peri-urban		
Date at symptom onset:		Date at first diagnosis:		
Clinician diagnosis of RA documented		Yes	No	

Date	RF	Positive	Negative
ANF	Hep B	HIV	
RF	Not done (ND)	Not found (NF)	
Date	RF	Positive	Negative
AntiCCP		ANF	

Disease Activity	At first diagnosis Date:	At last diagnosis Date:
Patients report of pain - Polyarticular(P) - Symmetrical(S) - Involvement of hands(H)		Pain – Intermittent/continuous
Number of swollen joints		
Number of tender joints		
Early morning stiffness		
Nodules		
Sicca Symptoms		
Deformities		

ESR		
CRP		
Hb		
MCV/MCH		
WCC		
Platelets		
Functional class		
Xray Joint Space Narrowing (JSN)		

Drug Therapy	Yes	Not Ever	Dose Max	Dose Current	Date Started	Date Stopped	Continuous/ Intermittent	Reason to Stop
Ridura								
Penicillamine								
Methotrexate								
1 <sup>st</sup> trial								
2 <sup>nd</sup> trial								
3 <sup>rd</sup> trial								
Sulphasalazine								
1 <sup>st</sup> trial								
2 <sup>nd</sup> trial								
3 <sup>rd</sup> trial								
Chloroquine								
Steroids								
NSAIDS								
- Brufen								
- Indocid								
- Voltaren								
- Naproxen								

Comorbid Disease	Yes	No	Date of Diagnosis	TOD/Mico-Macro	Evidence
Diabetes Mellitus					
Hypertension					
HIV					
Dyslipidemia					
Osteoarthritis					
Osteoporosis					
Other					
Total Number of Comorbid Conditions:					

Calcium Supplements	Vitamin D	Folate	Vitamin C
Losec	Statin	Aspirin	Paracetamol
Metformin	Sulphonylurea		Tramadol
HCTZ	Enalapril	Amlodipine	
Eltroxin	Ferrous Sulphate		
Fosomax			
Tears Naturelle			

Orthopaedic Surgery for RA	Yes	No
Number of Procedures		
Arthroscopy	Joint Replacement	Other