

HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION AND RHEUMATOID ARTHRITIS

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Witwatersrand, in partial fulfillment for the degree of Master of Medicine (Internal
Medicine)

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DECLARATION

I, Gareth Scott Tarr declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (Internal Medicine) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Theday of, 2012

DEDICATION

To my parents, Lorna and Flo and my beloved wife, Janine.

PRESENTATIONS ARISING FROM RESEARCH REPORT

Oral Presentations

1. HIV infection and rheumatoid arthritis.

South African Rheumatism and Arthritis Association Congress - 2009

2. Impact of HIV infection on disease activity in rheumatoid arthritis.

WITS, Faculty of Health Science Research Day - 22nd September 2010.

ABSTRACT

Objectives: To determine the impact of human immunodeficiency (HIV) infection on rheumatoid arthritis (RA) disease activity.

Patients & Methods: Retrospective record review of RA patients who HIV seroconverted, compared to a HIV negative RA control group. DAS28-ESR and -CRP scores were collected at the initial presentation (T_0), time when HIV diagnosis made (T_H) and the last clinic visit (T_L).

Results: Forty three HIV positive RA patients were included. At T_L disease activity was similar between the groups, despite methotrexate (MTX) being continued in only 11.6% of the HIV group (vs. 83.7% in the control group, $p=0.0002$). In the HIV group, all clinical parameters improved except the ESR, which accounted for the significantly higher DAS28-ESR compared to the DAS28-CRP at T_L ($p=0.004$). At T_L only 13.9% HIV patients had ongoing moderate to high disease activity.

Conclusion: Overall disease activity improved with HIV seroconversion in spite of stopping MTX in the majority of patients. The DAS28-ESR overestimated disease activity compared to DAS28-CRP following HIV seroconversion.

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NOMENCLATURE

ACR	American College of Rheumatology
AIDS	Acquired immuno-deficiency syndrome
ARA	American Rheumatism Association
CCP	Citrullinated protein
CCR5	C-C chemokine receptor type 5
CDAI	Clinical disease activity index
CDC	Centre for disease control
CQ	Chloroquine
CRP	C-reactive protein
CXCR4	C-X-C chemokine receptor 4
DAS28	Disease activity score – 28 joints
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism

GP	Glycoprotein
HAART	Highly active anti-retroviral therapy
HIV	Human immunodeficiency virus
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
LEF	Leflunomide
NS	Not significant
NSAID	Non-steroidal anti-inflammatory drug
MTX	Methotrexate
PCR	Polymerase chain reaction
PGA	Patients global assessment
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RNA	Ribonucleic acid
SD	Standard deviation
SDAI	Simplified disease activity index

SJC	Swollen joint count
SSZ	Sulfasalazine
T ₀	Time of initial RA diagnosis
T _H	Time when HIV diagnosis made
Th	T-helper cell
T _L	Time of last clinic visit
TJC	Tender joint count
TNF	Tumour necrosis factor
VAS	Visual analogue score
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION

1.1. Introduction

With the growing prevalence of human immuno-deficiency virus (HIV) in South Africa, it is now not an unfamiliar situation where patients with chronic medical conditions are co-infected with HIV. The complexity of individual diseases and their overlapping pathophysiology makes chronic disease interaction difficult to predict an outcome and consequently, choosing the appropriate therapy even more difficult. Currently, there are only a handful of published papers describing rheumatoid arthritis (RA) and HIV co-infection. The controversy over the exact effect of HIV on RA is still very debatable with varied clinical outcomes still being described, ranging from HIV induced RA remission (Bijlsma et al., 1988, Lapadula et al., 1997) to ongoing active synovitis (Black and Madhok, 1992, Ornstein et al., 1995).

1.2. Rheumatoid arthritis

1.2.1. INTRODUCTION

RA is a chronic, systemic, inflammatory, autoimmune disease that primarily involves the peripheral joints (Scott et al., 1987), but may also have extra-articular manifestations. Its primary target is the synovial tissue, which is characterized by leucocyte infiltration followed by hyperplasia and pannus formation (Bostrom et al., 2011). This will ultimately lead to erosion of cartilage and irreversible joint destruction, and if the process is left unchecked can cause significant disability due to functional impairment.

1.2.2. EPIDEMIOLOGY

The worldwide prevalence in the adult population is approximately 1%, with a female predominance (by a ratio of 3 to 1) (Gabriel, 2001), and an earlier onset in women frequently beginning in the childbearing years (Symmons et al., 1994). Compared to the African population, the prevalence of RA has been reported as approximately 0.9% for urban black South Africans (Beighton et al., 1975), and less than <0.1% in the rural black population. There are studies to suggest that there is a much greater female prevalence (6.9:1) and a younger age of onset (commonly less than 40 years of age) in our African patients, as compared to than the Western world (Tikly et al., 2003).

1.2.3. PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS.

There are multiple complex mechanisms contributing to the chronic inflammation seen in RA, and these mechanisms act both in parallel and sequentially within an affected joint (Lee and Weinblatt, 2001). The current understanding of the pathogenesis of the disease is still incomplete, but there is evidence to support the CD4 T cell playing a central role in initiating and perpetuating the chronic inflammation (Harris, 1990). Within the RA synovium, the T-lymphocytes form the bulk of the cells, more specifically the T-helper 1(Th1) CD4 cells, which upon activation by as yet unknown antigens; drive a pro-inflammatory process characterized by activation and proliferation of synovial and endothelial cells, recruitment and activation of additional pro-inflammatory cells, secretion of cytokines (tumour necrosis factor [TNF], interleukin [IL]-1, IL-2, interferon [IFN], and IL-12) and

proteases from macrophages and fibroblast-like synovial cells, and autoantibody production (Berner et al., 2000). These cytokines can then induce further controlled expression of other cytokines, cell adhesion molecules, immune-regulatory molecules, and other pro-inflammatory mediators. By comparison, Th2 CD4 cells down-regulate the inflammatory cascade by causing secretion of anti-inflammatory cytokines IL-4 and IL-5, which promote humoral immunity and are involved in atopy (Schulze-Koops and Kalden, 2001). Additional antigens also recognized to activate T cells include: Type II collagen, cartilage antigen glycoprotein (gp) -39, immunoglobulin (Ig) G, and citrullinated proteins and peptides (Cope et al., 1999, De Rycke et al., 2004, Grinnell et al., 2005, He et al., 2000).

Other than CD4 T cells, macrophages, fibroblasts, osteoclasts, neutrophils, and B lymphocytes all add to the chronic inflammation. Specific antibody production produced by the B lymphocytes, include rheumatoid factor (RF) and anti-citrullinated peptide (anti-CCP) antibodies, whose presence indicates a higher rate of bone erosions and extra-articular manifestations.

The hypertrophic, inflamed synovium known as the pannus eventually leads to cartilage destruction at the cartilage-pannus junction, via direct invasion of the synovial cells into the cartilage (Bostrom et al., 2011), and rarely by abscess formation from neutrophils and areas of rapid chondrolysis. Associated with the cartilage breakdown is subchondral bone destruction, from the action of osteoclasts, chondroclasts together with metalloproteinase all activated by synovial cytokines.

1.2.4. DIAGNOSIS

Rheumatologists are passionate about classification criteria and nomenclature for various rheumatic diseases, as they help with standardisation of disease diagnosis and are useful in clinical research. Over the decades, multiple different 'classification' criteria have been developed for RA, only to be superseded with the progressive improvement of criteria to update the shortcomings of previous classification systems.

One of the first classification criteria for RA was proposed in 1958, by the American Rheumatism Association (Ropes et al., 1958), which was based on experiences of the committee members, a literature review of recent surveys, and case reviews of many hundreds of patients scattered over the United States Of America. This version of the classification criteria was extensively used, but as time passed and the knowledge of rheumatic disorders increased many forms of arthritis previously misdiagnosed could be separately classified. This brought about a revision of the criteria which would increase the sensitivity and specificity of the diagnostic criteria for the identification of RA, and was known as the 1987 American College of Rheumatology (ACR) criteria (Arnett et al., 1988).

The latest criteria for RA, the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria (Aletaha et al., 2010), improved the inadequacy of the 1987 ACR criteria's inability to recognise and diagnose early undifferentiated arthritis with an increased risk of erosive disease of RA.

This study was concluded before this most recent publication and was therefore based on the 1987 ACR criteria (Arnett et al., 1988), which required more than 4 criteria to be met and present for a duration longer than six weeks, then RA is the probable diagnosis. The criteria include: (1) Morning stiffness, lasting for more than one hour before maximal improvement; (2) Arthritis of 3 or more joint areas; (3) Arthritis of hand joints; (4) Symmetric arthritis; (5) Rheumatoid nodules; (6) Serum RF and; (7) radiographic changes of periarticular osteopenia with marginal erosions.

1.2.5. ASSESSMENT OF DISEASE ACTIVITY

There are numerous composite formulations available to assess disease activity in RA, e.g. Disease Activity Score (DAS), 28-joint DAS (DAS28 – erythrocyte sedimentation rate [ESR] or – C-reactive protein [CRP]), Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) (see Figure 1.1).

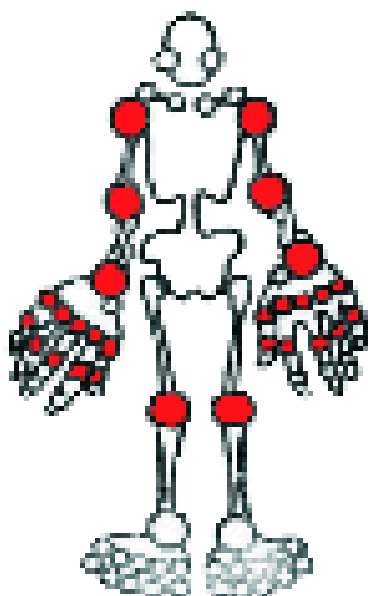


Figure 1.1 DAS28 joint count homunculus

These scores provide a means of monitoring disease activity, allowing for treatment to be adjusted accordingly. The SDAI is the sum of the 28 swollen joint count (SJC), the 28 tender joint count (TJC), the patient global assessment (PGA) and the physician assessment of disease activity using a 10cm long visual analogue score (VAS), and the CRP value in mg/dl (Aletaha et al., 2005). The CDAI is similar to the SDAI, but without the CRP value and more emphasis on the clinical assessment. The initial DAS score comprised the: Ritchie articular index (joint score based on tenderness, where all joints are examined, but the proximal interphalangeal; metacarpophalangeal; metatarsophalangeal; temporomandibular; sternoclavicular; and acromioclavicular joints are calculated as a single unit); 44 swollen joint count; ESR and the PGA. Once it was established that a 28 joint count performed as well as more extensive joint counts, the DAS evolved into the DAS28 (Prevoo et al., 1995). The DAS28 scoring system, which is used at the Chris Hani Baragwanath Academic Hospital Rheumatology Unit, is a composite score made up of multiple variables including: SJC, TJC, PGA, and either ESR or CRP value (van der Heijde et al., 1992).

Formulae:

Equation 1.1 Calculation of DAS28-ESR

$$\text{DAS28-ESR} = 0.56 \cdot \sqrt{\text{TJC}} + 0.28 \cdot \sqrt{\text{SJC}} + 0.7 \cdot \ln \text{ESR} + 0.014 \cdot \text{PGA}$$

Equation 1.2 Calculation of DAS28-CRP

$$\text{DAS28-CRP} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.36 \cdot \ln (\text{CRP} + 1) + 0.014 \cdot \text{PGA} + 0.96.$$

Disease activity is categorized as follows: ≤ 2.6 remission, ≤ 3.2 low disease activity, 3.2 – 5.1 moderate disease activity and ≥ 5.1 high disease activity (Aletaha et al., 2005).

1.2.6. TREATMENT

The approach to RA treatment is improving as the understanding of the pathophysiology evolves. The principles of treatment are to relieve pain, improve function, control joint inflammation and thereby reduce irreversible joint damage, and to prevent/treat complications, including drug complications. The modalities available include non-pharmacological therapy (i.e. education, physiotherapy, and occupational therapy), drugs and surgery. Pharmacological agents include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying anti-rheumatic drugs (DMARDs), and both synthetic and biologic DMARDs. It is vital to definitively diagnose RA early, as joint damage occurs early on in the disease

process and treatment with a DMARD should be implemented as soon as possible (Goekoop-Ruiterman et al., 2005). Monitoring of disease with composite scores (e.g. DAS28) can help with clinical decision making to achieve tight control.

Disease-modifying anti-rheumatic drugs form the mainstay of drug treatment in RA and can be divided into non-biologic and biologic drugs, where both classes provide immunosuppressive effects through different mechanisms. Synthetic DMARDs include chloroquine (CQ), sulfasalazine (SSZ), methotrexate (MTX), and leflunomide (LEF). MTX inhibits deoxyribonucleic acid (DNA) dihydrofolic acid reductase thereby interfering with DNA synthesis, repair and cellular replication, and if control is insufficient with MTX alone, other DMARDs are added to achieve tight control. MTX is considered the “anchor drug” in RA treatment and is continued in combination regimens in patients with poor disease control. Although MTX being the principal agent in RA treatment, there are studies to suggest that LEF and SSZ are as effective MTX (Donahue et al., 2008). The ACR recommendations prefer MTX and LEF for active disease with features of poor prognosis (Saag et al., 2008). Biologic drugs target cytokines or their receptors and include the TNF inhibitors, etanercept, infliximab, and adalimumab, the IL-1 receptor antagonist, anakinra, the IL-6 receptor antagonist, tocilizumab, the CTLA4-Ig fusion protein, abatacept, and the anti-CD20 B-cell monoclonal antibody target, rituximab. The use of DMARDs is not without toxicity and it is important to monitor for infections, liver toxicity, renal toxicity, bone marrow suppression and malignancies. The DMARD agents available at the Chris Hani Baragwanath Rheumatology Unit are almost exclusively the synthetic agents, where MTX forms the pivotal drug in most cases.

1.3. Human immunodeficiency virus

1.3.1. OVERVIEW

Human immunodeficiency virus is a blood-borne virus, which belongs to the family of human retroviruses (retroviridae) and the subfamily of lentiviruses. There are two distinct species of HIV, namely HIV-1 and HIV-2 subtypes, superficially similar but with unique replication processes. The HIV-1 subtype seems to predominate in the developed world (Taylor and Hammer, 2008). Infection with HIV progressively destroys the CD4 T cells resulting in immune impairment, increasing the risk of infections and malignancies, proportional to the peripheral CD4 T cell count. Disease can vary from asymptomatic to acquired immuno-deficiency syndrome (AIDS), which is defined by either the Center for Disease Control (CDC) or World Health Organization (WHO) staging classification (CDC, 1999, WHO, 2007).

The worldwide incidence of HIV/AIDS, according to United Nations AIDS (UNAIDS), in 2010 was estimated at 33 million people, almost 1% of the global adult population aged 15-49 yrs. The pandemic is still highest in Africa, with an estimated 22.5 million or 5% of the adult population found in sub-Saharan Africa (UNAIDS, 2010). Recent HIV statistics in our study population, the Gauteng province has a prevalence of 10.3% and an incidence highest amongst females aged 25-29 years of 32.7% and males 30-34 years of 25.8% (Rehle et al., 2010).

1.3.2. PATHOPHYSIOLOGY OF HIV

There are various stages in the HIV life cycle, beginning with viral transmission either via sexual intercourse, perinatal transmission or exposure to contaminated blood. In low socioeconomic regions, vaginal intercourse is responsible for 70-80% of HIV/AIDS cases (Adler, 2001). Following viral transmission across a mucous membrane, the HIV is phagocytosed by antigen presenting cells (i.e., dendritic cells, macrophages) and transported to lymph nodes and peripheral blood where they are presented to the cell-mediated immune system, i.e., CD4 T cells. There are envelope proteins on the surface of the HIV, gp-120 and gp41, which bind to chemokine receptors on the surface of the CD4 T cells, namely C-C chemokine receptor type 5 (CCR5) and C-X-C chemokine receptor 4 (CXCR4). After the binding of these receptors, it allows fusion of the membranes followed by release of HIV ribonucleic acid (RNA) and enzymes into the CD4 T cell. The HIV RNA is then converted to single strand DNA by the viral enzyme reverse transcriptase. Subsequently, the single strand of DNA is then replicated by host cell enzymes into double stranded HIV DNA which is taken up into the host cell nucleus and is integrated into CD4 T cell DNA. The host cell then produces HIV RNA and HIV proteins, which are assembled in the cytoplasm of the host cells into virions which bud off from the cell membrane forming viruses that can infect other CD4 T cells (Cohen et al., 2011).

The consequence of HIV infection is progressive damage to immune system, specifically cell-mediated immunity, but humoral immunity is also affected. The HIV targets the CD4 T cells with an inversion of the normal CD4/CD8 T cell ratio (Schechter et al., 1987). Contributing to the impaired cell-mediated immunity is the

cytokine dysregulation, with a shift from Th1CD4 to Th2 CD4 predominant cytokines. Therefore, there is a decrease in pro-inflammatory cytokines: IL-2; IFN and TNF; and an increase production of anti-inflammatory cytokines: IL-4; IL-5 (Clerici and Shearer, 1993). Humoral immunity derangement is characterized by B cell hyperplasia with the secretion of antibodies and a consequent hypergammaglobulinemia, especially IgG and IgA.

1.3.3. DIAGNOSIS

The available tests to diagnose HIV include antibody testing (rapid antibody test, enzyme-linked immunosorbent assay [ELISA], and Western blot assay) and testing for HIV itself (polymerase chain reaction [PCR] and culture). Diagnosis of HIV can be confirmed in high prevalence areas (>10% incidence) with two positive rapid antibody or ELISA tests, according to the WHO criteria (Martin and Sim, 2000). The investigation most often used in our clinic is the ELISA, which is a serological test used to detect anti-HIV IgG/IgM antibodies.

1.3.4. TREATMENT

After HIV seroconversion, patients should be referred to a clinician with HIV expertise as this has proven to offer better outcomes for the patient (Kitahata et al., 1996). The principal therapy to prevent immune deterioration is to initiate highly active anti-retroviral therapy (HAART), and prophylaxis for opportunistic infections should also be considered. The primary goals for initiating HAART are to: reduce HIV-associated morbidity and mortality; restore immunologic function; suppress plasma HIV viral load; and to prevent HIV transmission. The WHO guidelines have recently been

amended following positive results with earlier HAART initiation trials (Severe et al., 2010, Sterne et al., 2009), and now advocate initiation with HAART when the CD4 count is less than 350cells/ μ L (WHO, 2010). Until recently, HAART was initiated only when the patient CD4 count was less than 200cells/ μ L in the South African state sector. However, these guidelines have recently changed to include early initiation of HAART in pregnant women and patients co-infected with tuberculosis with a CD4 count <350cells/ μ L, initiation if WHO stage IV, and if proven multi-drug resistant/extreme-drug resistant tuberculosis irrespective of CD4 count.

1.4. Rheumatoid arthritis and HIV co-infection

As mentioned previously, the controversy over the exact effect of HIV on RA is still debatable. There are only a handful of published case reports describing the HIV co-infection in RA patients, with various outcomes observed and the issue of DMARD treatment being a continuously problematic question.

The first case described was in a 60 year old Dutch man who presented in 1985 with a severe polyarthritis, morning stiffness for longer than 2 hours, weight loss (8kg), elevated ESR of 51mm/hr, RF negative, no erosions present on x-rays, and a subcutaneous nodule biopsied which showed an inner necrotic core with destroyed collagen and fibrin with a palisade arrangement of mononuclear cells (Bijlsma et al., 1988). Definitive RA was diagnosed and he was started on intramuscular gold to which he responded as evident by a decrease in the number of affected joints, weight

gain and a fall in ESR to 12mm/hr. The following year his physical condition deteriorated and he now had clinical evidence of oral candida, generalized lymphadenopathy, hepatosplenomegaly with positive serology for hepatitis B, cytomegalovirus, Epstein-Barr virus, and a positive ELISA for HIV. However, despite his deteriorating physical condition, there was no evidence of active synovitis, and thus, the question arose “Does AIDS ‘cure’ rheumatoid arthritis?”

A further case was that of a American 63 year old female who diagnosed with RA in 1983 after presenting with a symmetrical polyarthritis affecting the small joints of the wrist and hands, associated with morning stiffness, and a positive RF (Calabrese et al., 1989). She was initially doing well on aspirin and intermittent injections of adrenocorticotrophic hormone, until June 1984 when she was admitted for a week with fever, pharyngitis, diarrhoea, abdominal cramping, macular rash and lymphadenopathy. From August to October 1984 she complained of ‘new’ sicca symptoms and her serology was repeated revealing a positive RF titre (1:5000), positive ANA titre (1:640), and she was then diagnosed with Sjögren’s syndrome and Systemic lupus erythematosus and was initiated on aspirin and hydroxychloroquine. In 1985 she consulted a second rheumatologist who diagnosed RA with Felty’s syndrome and Sjögren’s syndrome, based on evidence of increasing sicca symptoms, fatigue, generalised lymphadenopathy, no active synovitis at that time, positive RF, positive ANA, and cortical bone erosions of the metacarpophalangeal joints on repeated x rays. She was continued on hydroxychloroquine. Her husband was diagnosed HIV positive in 1987, following a contaminated blood transfusion he

received in 1984. Later in 1987, she tested HIV positive, had no active synovitis, but persistent sicca symptoms that lead to a salivary gland biopsy that was consistent with Sjögren's syndrome.

A 58 year old American man diagnosed with RA, fulfilling all 7 of the 1987 ACR criteria, had been receiving treatment with cyclophosphamide and corticosteroids for rheumatoid vasculitis, until he was diagnosed HIV positive by ELISA and Western blot after presenting with oral candidiasis and *Pneumocystis carinii* pneumonia (Kerr and Spiera, 1991). Despite his immunosuppression, it was noted that he continued to have active joint disease throughout his illness.

In 1986, a 28 year old HIV positive Englishman presented with arthritis of his knees and feet, which developed into a RF negative symmetrical polyarthritis involving the small joints of the hands as well, and associated with morning stiffness (Jaffer, 1991). He was found to be HLA-B27 positive, but there was no report of backache, or evidence of psoriasis. The patient was diagnosed with RA and was treated unsuccessfully with NSAIDs and steroids, with the eventual development of periarticular osteopenia and erosions in keeping with his diagnosis. His unremitting active synovitis continued until his death from an upper gastrointestinal bleed secondary to Kaposi's sarcoma.

In January 1991, a 48 year old female heroin user was admitted into New York City Hospital with asthma, but also reported symmetrical joint pains (involving knees,

hands, and wrists) with a history of morning stiffness and diffuse joint swelling (Ornstein et al., 1995). She had previously being diagnosed as RA after having a positive RF and typical x-ray changes. Her current therapy consisted of steroids and NSAIDs, as she developed a rash secondary to intramuscular gold. Later that year she was admitted and treated for pneumocystis carinii pneumonia. At that time she was tested for HIV and found to have a reactive result, and CD4 count was 250cells/ μ L. She was started on HAART and continued on steroids with trimethoprim/sulfamethxazole; however there was ongoing polyarthritis with 2 hour long morning stiffness. Her arthritis continued unabated and by 2004 she had developed a symmetrical deforming polyarthritis involving her hands and wrists with active synovitis and x-rays revealing joint space narrowing with erosions. She was started on hydroxychloroquine, however active synovitis of her hands persisted.

In 2005, a 45 year old Spanish women, known to be HIV positive since 1999 on HAART, presented with a polyarthritis and established hand deformities, morning stiffness for 2 hours, ESR of 75mm/hr, CRP was 48 mmol/L, CD4 count 422 cells/ μ L, polyclonal hypergammaglobulinemia, and positive RF titre (1:5000) (Azeroual et al., 2008). She was started on NSAIDs and hydroxychloroquine and clinical remission was achieved at follow up. Interestingly, RA was diagnosed after 6 years of HIV infection and her arthritis was controlled with minimal DMARD usage. But once her CD4 count reached normal levels, it was noted that her RA symptoms returned, thus immune reconstitution resulted in active RA disease.

The above case reports demonstrate the complexity of the RA and HIV relationship and only by re-examining their individual pathophysiologies can we hope to understand the combined disease interaction.

The RA disease process is characterised by an inflamed joint mediated by a high proportion of T-lymphocytes, of which the CD4 T cells predominant with an increase of Th1 cytokines. Notable Th1 CD4 cytokines are IL-1; IL-6 and TNF- α , which initiate a pro-inflammatory destructive process (Bingham, 2002). Conversely, HIV causes an immunosuppressive state mainly through the destruction of CD4 T cells and is associated with other chronic immune changes such as failure of the cytotoxic T cells to inhibit viral replication, apoptosis, nonspecific B cell proliferation with an associated hypergammaglobulinemia, destruction of natural killer cells and a cytokine shift from pro-inflammatory to anti-inflammatory. It has been postulated that this cytokine shift from Th1 cell to Th2 cell dependant cytokines may be responsible for HIV induced RA remission (Wegrzyn et al., 2002). The Th2 CD4 cytokines include IL-4, IL-10, which are mainly anti-inflammatory and are responsible for activation of the humoral immune response, resulting in non-specific B cell proliferation and the hypergammaglobulinemia. Importantly, previous studies have shown an elevated ESR is associated with high level of plasma proteins (Talstad et al., 1983), and thus, an elevated ESR may affect the DAS28-ESR score but not the DAS28-CRP. The Th2 cytokine profile which predominates in HIV infected individuals may reflect why these patients have decreased disease activity. However, this may not be the only scenario as T cell independent factors, such as autonomous fibroblast activation, may be

responsible for ongoing inflammation and therefore remission might not be the obvious outcome.

Another complex issue facing HIV positive patients with RA is the concern of added immunosuppressive therapy. There is limited information concerning the safe use of MTX in these patients and early reports with the use of MTX in psoriatic arthritis showed an increase in the incidence of opportunistic infections and accelerated HIV disease (Duncan et al., 1998, Maurer et al., 1994), but later reports have been more promising (Maurer et al., 1994). Currently, no agreement exists as for the continual treatment of these patients and it has thus been the decision of Chris Hani Baragwanath Rheumatology Unit to stop MTX in all RA patients, especially those with a CD4 count < 100cells/ μ L, and switch them to either: SSZ, CQ, or a combination of the two or no treatment in the case of clinical remission.

There are however 4 cases in the literature reporting success with the use of biologic agents. Aboulafia et al reported on the benefit of etanercept in a HIV positive patient with psoriatic plaques and arthritis not on MTX (Aboulafia et al., 2000). Gaylis et al described improvement in reactive arthritis symptoms in a HIV patient refractory to NSAIDs treated with infliximab (Gaylis, 2003). Bartke et al had a similar patient with HIV and psoriatic arthritis having significant improvement of symptoms with infliximab (Bartke et al., 2004). Finally Kaur et al reported improvement in disease activity with

the use of etanercept in a patient failing combined therapy including CQ, SSZ and corticosteroids (Kaur et al., 2007).

1.5. Aim of the study

In the absence of any studies in a HIV endemic region, like South Africa, the aim of this presentation was to assess the impact of HIV infection on RA clinical activity seen at Chris Hani Baragwanath Academic Rheumatology Unit. The primary objective was to assess the changes in disease activity with HIV seroconversion, and the secondary objective was to compare the difference between DAS28-ESR and DAS28-CRP following seroconversion.

CHAPTER 2: PATIENTS AND METHODS

2.1. Patients

Inclusion criteria for the study group, henceforth called the HIV group, included patients 1) fulfilled criteria for RA (Arnett et al., 1988), 2) who initially tested HIV negative at the time of RA diagnosis and subsequently contracted HIV infection, and 3) in whom disease activity parameters (SJC, TJC, PGA, ESR, CRP) had been recorded since 1994. Exclusion criteria included 1) incomplete data, and 2) patients who presented simultaneously with RA and HIV. A HIV group was matched to a control group for sex and age (± 5 years).

2.2. Methods

Data from three specific periods was collected to analyse the impact of HIV on RA, i.e. T_0 - time of initial RA diagnosis, T_H – first visit after HIV diagnosis, and T_L - the last clinic visit up until 31/12/2008. Data abstracted from case records included: SJC, TJC, PGA based on the visual analogue score, DAS28-ESR, DAS28-CRP, CD4 counts, chronic infections, malignancies, and medications. RF was assayed by nephelometry (Siemens Healthcare Diagnostics, BN Prospec Nephelometer, Newark, USA) and a value greater than 15 IU/ml was considered positive.

HIV testing was routinely performed annually in the clinic because of the high incidence of HIV in the community, the unknown risk of HIV and continued MTX treatment, or when there was a clinical suspicion.

2.2.1 CALCULATION AND EVALUATION OF DISEASE ACTIVITY

The DAS28-ESR and DAS28-CRP formulas were used to calculate disease activity.

Disease activity was categorized as follows: ≤ 2.6 remission, ≤ 3.2 low disease activity, $3.2 - 5.1$ moderate disease activity and ≥ 5.1 high disease activity. (See Equation 1.1 and 1.2)

2.2.2. STATISTICS

Data was captured on a Microsoft Excel spreadsheet and then transferred to GraphPad InStat (version 3) software, which was used for statistical analysis. To compare continuous variables the Student's T-test was used, and for categorical variables, the Chi-square test or the two-tailed Fisher's exact test was applied.

Correlation of continuous variables was analysed by using the Pearson's correlation test. A p-value of <0.05 was considered significant.

CHAPTER 3: RESULTS

3.1. HIV group

A total 1712 had RA and documented disease activity parameters since 1994 in the out-patient records. Of these 85 patients were HIV positive, but only 43 of those met the inclusion criterion of having contracted HIV after the diagnosis of RA was made (see Figure 3.1). Hence, the overall prevalence of HIV in this cohort of RA patients was 4.9%.

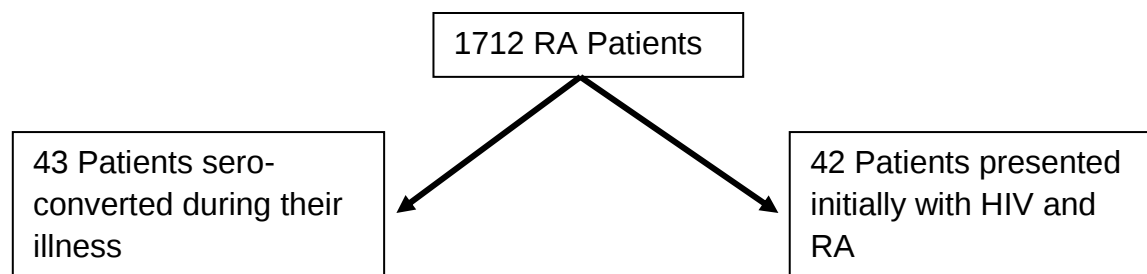


Figure 3.1 HIV prevalence in RA patients

Of the 43 patients, 39 (90.7%) were female and 4 males (9.3%) with a mean(SD) age of 47.1(10.1) years (range 23-65), mean(SD) age of RA diagnosis 36.4 (12.1) years (range 8-60), mean(SD) RA disease duration 10.5 (8.4) years (range 1-38), mean(SD) HIV duration of 2.9 (2.0) years (range 0-8), and the mean(SD) RF at T_0 was 415 (839) IU/ml (see Table 3.1). At T_0 , only 20 (46.5%) patients had been initiated on MTX based therapy, but this number increased to a total of 34 (79%) patients on MTX treatment by T_H . At this point, T_H , DMARD therapy was de-

escalated to reduce the risk of opportunistic infections due to the combined immunodeficiency caused by HIV infection and MTX. Methotrexate treatment was stopped in all but 5 patients. Patients were continued on other DMARDs, like SSZ and CQ. Five patients remained on MTX in spite of HIV seroconversion. Six patients were started on HAART with a mean (SD) duration of 1.5 (1.2) years treatment, range (6 months to 4 years).

Table 3.1 Demographic table comparing HIV and control group

	HIV Group (n=43)	Control Group (n=43)	p Value
Mean (SD) age in years	47.1 (10.1)	45.7 (8.0)	NS
Mean (SD) age of RA diagnosis in years.	36.4 (12.1)	38.5 (8.0)	NS
Mean (SD) RA disease duration in years	10.5 (8.4)	7.1 (3.8)	0.02
Mean (SD) HIV disease duration in years	2.9 (2.0)	-	-
RF (SD) IU/ml	414.7 (838.93)	446.54 (650.89)	NS
% RF positive at baseline	88.3%	74.4%	-

NS = Not significant; RA = Rheumatoid arthritis; RF = Rheumatoid factor.

As shown in Table 3.2 and Figure 3.2, all markers of disease activity and the composite DAS28-ESR and DAS28-CRP scores, except the ESR, decreased significantly from T_0 to T_H . There was a numerical increase in the ESR, but this did not reach statistical significance. There was a further decline in PGA, DAS28-ESR,

and DAS28-CRP from T₀ to T_H, in spite of the majority, 29 of 34 patients (85%) coming off MTX.

Table 3.2 Summary of HIV group results

Variable	T₀ mean (SD)	T_H mean (SD)	p value *	T_L mean (SD)	p value **
SJC	5.5 (4.3)	0.9 (1.8)	<0.0001	0.6 (1.7)	NS
TJC	8.1 (5.3)	2.0 (4.1)	<0.0001	0.8 (2.3)	NS
PGA	52.4 (22.9)	24.4 (19.8)	<0.0001	15.5 (17.4)	0.04
ESR	41.7 (25.4)	47.0 (30.7)	NS	50.5 (34.7)	NS
CRP	37.1 (40.1)	12.6 (15.8)	0.002	12.3 (12.0)	NS
DAS28-ESR	5.2 (1.3)	3.4 (0.9)	<0.0001	2.9 (0.9)	0.01
DAS28-CRP	4.9 (1.1)	2.6 (1.0)	<0.0001	2.2 (0.8)	0.02

*T₀ vs. T_H; ** T_H vs. T_L; T₀ = Time of initial RA diagnosis; T_H = Time when HIV diagnosis made; T_L = Time of last clinic visit; SJC = Swollen joint count; TJC = Tender joint count; PGA = Patient global assessment; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease activity score 28 joint count; NS = Not significant.

Table 3.3 Summary of Remission in the HIV group

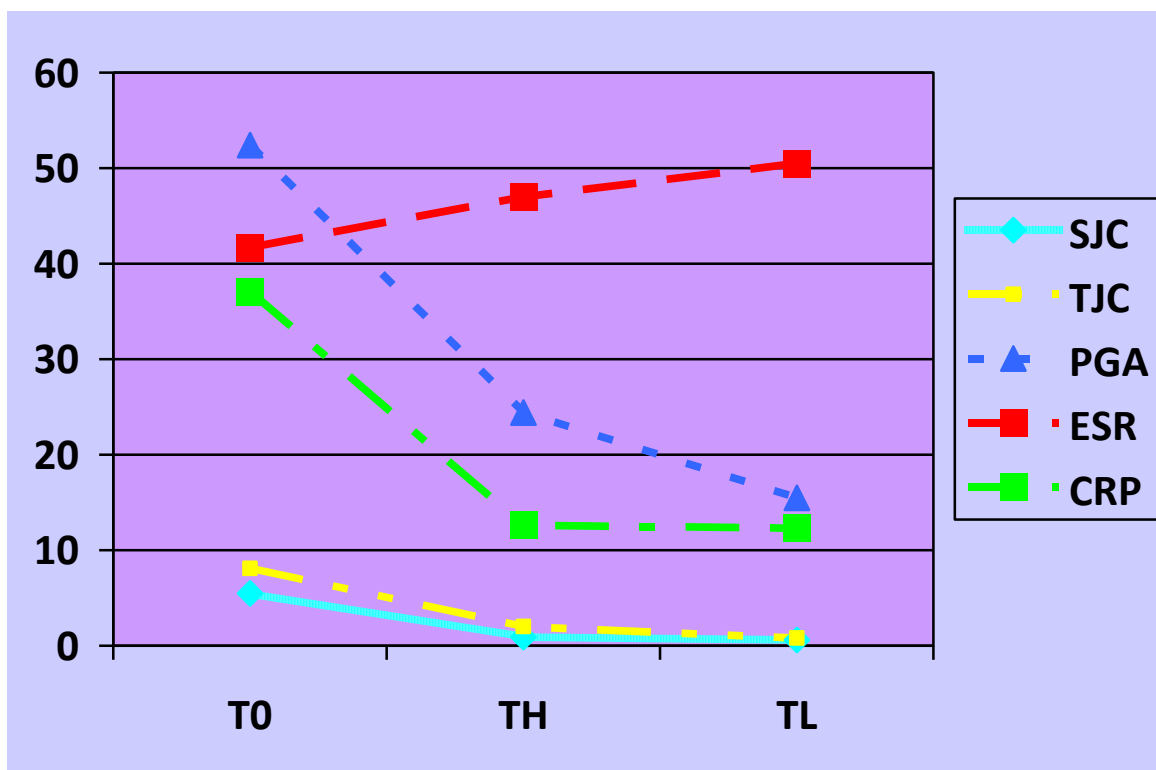
	DAS28-ESR Remission (≤2.6)	DAS28-CRP Remission (≤2.6)	p value
T₀	2/43	2/43	NS
T_H	7/43	23/43	0.0006
T_L	11/43	32/43	0.0001

T₀ = Time of initial RA diagnosis; T_H = Time when HIV diagnosis made; T_L = Time of last clinic visit; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease activity score 28 joint count; NS = Not significant.

At T_H DAS28-ESR (SD) showed moderate disease activity with a mean of 3.4 (0.9) when compared to DAS28-CRP (SD) mean of 2.6 (1.1), indicating remission. At T_L , DAS28-ESR (SD) had a mean of 2.9 (0.9) reflecting low disease activity and DAS28-CRP (SD) mean of 2.2 (0.8) indicating remission (See Table 3.2). Moreover, there was no difference in the proportion of patients in remission as compared by the ESR and CRP at T_0 (see Table 3.3), but at both T_H and T_L , the percentage of patients in remission was significantly higher as measured by the DAS28-CRP compared to the DAS28-ESR. When DAS28-ESR was compared to DAS28-CRP at each point, there was no statistical difference at T_0 ($p=0.36$), but DAS28-ESR was significant higher at T_H ($p=0.0005$) and T_L ($p=0.004$), being 31.8% higher than DAS-28-CRP at T_L . Graphic representation shows the progressive divergence between the DAS28-ESR and DAS28-CRP scores with time, and that the DAS28-ESR based score overestimated disease activity at each point compared to DAS28-CRP (See Figure 3.3).

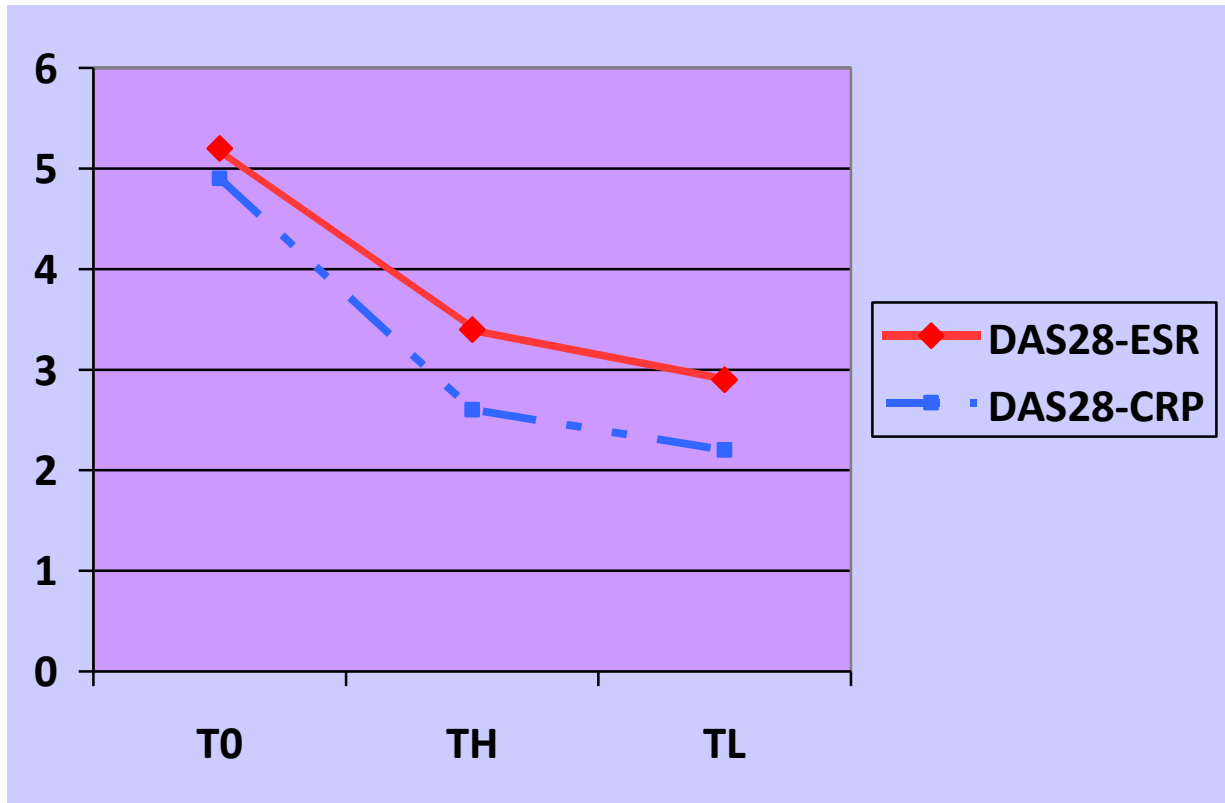
In the 31 patients in whom CD4 counts were available at T_H the mean (SD) count was 414.7 (201.17) cells/ μ l and at T_L the mean (SD) CD4 count in the 36 patients in whom there were results was 390.7 (293.7) cells/ μ l. Subgroup analysis comparing CD4 counts in those patients who had achieved at least low disease activity ($n=30$) to those who continued to have moderate to high disease activity ($n=6$) showed no statistical difference (mean (SD) 419.1 [299.7] vs. 213.6 [103.7], respectively).

Only 6 patients had been commenced on HAART with a mean (SD) duration of 1.6 (1.3) years. No change in disease activity had been noticed in response to therapy.



T₀ = Time of initial RA diagnosis; T_H = Time when HIV diagnosis made; T_L = Time of last clinic visit; SJC = Swollen joint count; TJC = tender joint count; PGA = Patient global assessment; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease activity score 28 joint count.

Figure 3.2 Changes in disease activity markers in the HIV group over time



T_0 = Time of initial RA diagnosis; T_H = Time when HIV diagnosis made; T_L = Time of last clinic visit;
DAS28 = Disease activity score 28 joint count.

Figure 3.3 Changes in DAS28 scores in the HIV group over time

3.2. Control group

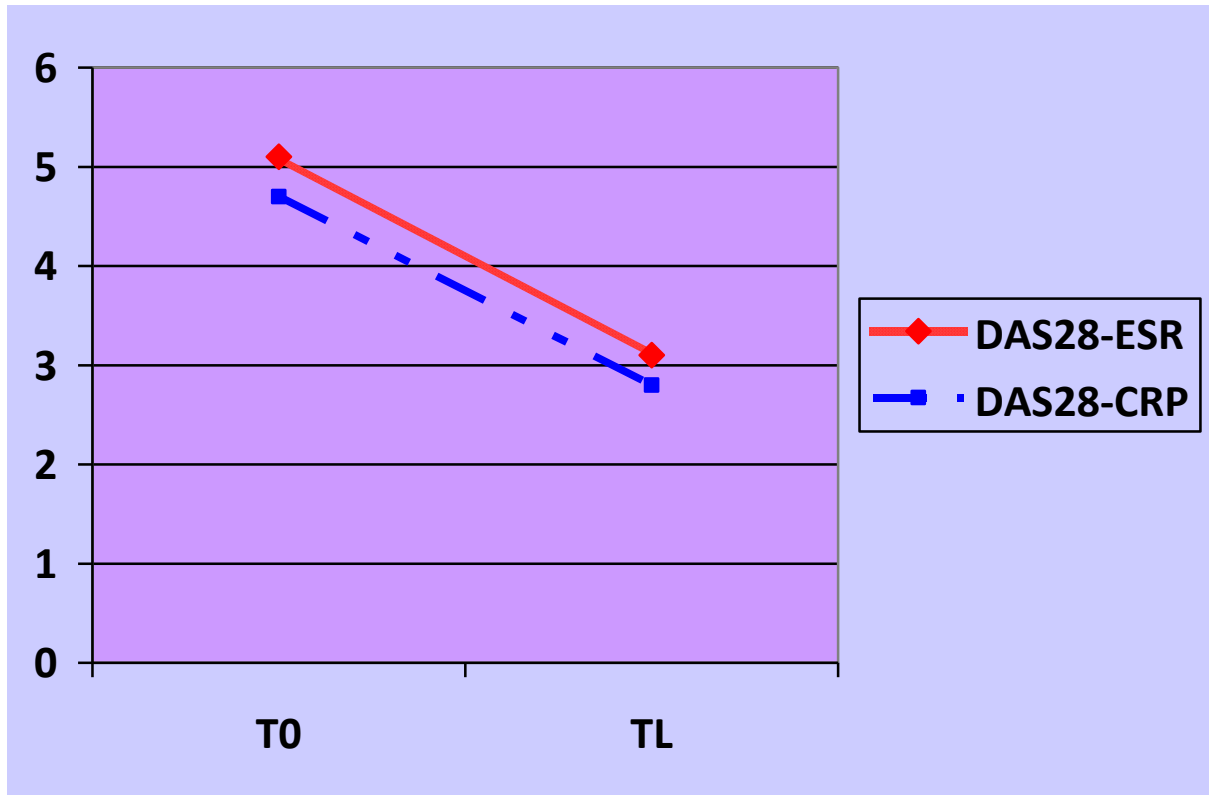
There were 43 patients in the control group with a mean (SD) age of 45.7(8.0) years, mean (SD) age of RA diagnosis of 38.5 (8.0) years, and a mean (SD) RA disease duration of 7.1(3.8) years (see Table 3.1). The control groups' SJC, TJC, PGA, CRP, ESR, were compared according to two time periods under review, i.e. T_0 - time of initial RA diagnosis, and T_L - the last clinic visit up until 31/12/2008.

At T_0 , 19 (44.2%) patients had been initiated on MTX based therapy, and this increased to 36 (83.7%) patients on MTX treatment by T_L (see Table 3.8). All results, including the DAS28-ESR and DAS28-CRP, showed significant improvement between the two data capture periods (See Table 3.4 and Figure 3.4). The RF (SD) of 35 (81.4%) patients at T_0 was 446.5 (650.89) IU/ml and at T_L only 17 (40%) of patients had a recorded RF (SD) which was 307 (660.8) IU/ml, a non significant change.

Table 3.4 Summary of control group results

Variable	T₀ mean(SD)	T_L mean(SD)	<i>p</i> value
SJC	5.1.(3.6)	1.2(1.5)	<0.0001
TJC	7.2(6.0)	1.6(2.8)	<0.0001
PGA	50.0(16.3)	27.3(18.7)	<0.0001
ESR	41.2(28.2)	24.4(15.2)	0.0016
CRP	34.2(44.9)	13.4(12.9)	0.0139
DAS28-ESR	5.1(1.1)	3.1(1.0)	<0.0001
DAS28-CRP	4.7(1.0)	2.8(1.0)	<0.0001

T₀ = Time of initial RA diagnosis; T_L = Time of last clinic visit; SJC = Swollen joint count; TJC = Tender joint count; PGA = Patient global assessment; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease activity score 28 joint count.



T_0 = Time of initial RA diagnosis; T_L = Time of last clinic visit; DAS28 = Disease activity score 28 joint count.

Figure 3.4 Changes in DAS28 scores in the control group over time

3.3. Comparison between the study and control group

The only significant difference between the two groups at T_0 , was the mean (SD) disease duration with the HIV group having a mean of 10.5 (8.4) and the control group mean of 7.1 (3.8) (See Table 3.1). Comparison of the disease states at T_0 revealed no significant differences, whether the DAS28-CRP or the DAS28-ESR calculation was used (see Table 3.5). At T_L most comparisons between the HIV and control groups resulted in non-significant values, except the ESR, PGA, and the DAS28-CRP. Due to improving disease activity in the HIV group, the PGA scores also improved significantly more than the control group. A key figure distinguishing the two groups was the DAS28-CRP, which revealed a mean (SD) in the HIV group of 2.2 (0.8), remission, compared to control group mean of 2.8 (1.0), active disease. This value is significant and represents remission in the HIV group without DMARD therapy compared to active disease in the control group on therapy. An increasing % difference between the DAS28-ESR and DAS28-CRP was noted with time; however, it was more marked in the HIV group than the control group. The initial % difference at T_0 was 3% for HIV group and 4% for the control group, but then at T_L the HIV group was 7% and the control group was 3%. There was clearly an increase divergence between the DAS28-ESR and DAS28-CRP values with time which accounted for the widening % difference, further indication that the DAS28-ESR was overestimating disease activity and was being influenced by additional factors other than RA inflammation. The comparison of the number of patients in different disease category states, based on either the DAS28-ESR or –CRP, was not statistically significant (see Table 3.6 and 3.7).

A vital consideration when interpreting these results is to take into account the differences in DMARD trends at the different time intervals. At T₀, 20 (46.5%) HIV patients and 19 (44.2%) control patients were on MTX, a non significant difference. Similarly at T_H, there was no significant difference in the usage of MTX in the HIV group (before de-escalation of treatment), compared to the DMARD use in the control group at T_L. However, following the diagnosis of HIV infection, the majority of patients in the HIV group came off MTX, and only 5 patients remained on the drug at T_L, compared to the 36 (83.7%) patients in the control group (p=0.0002) (see Table 3.8).

Table 3.5 Comparison between the HIV and control group

Variable	T₀HIV mean (SD)	T₀Control mean (SD)	p value *	T_L HIV mean (SD)	T_L Control mean (SD)	p value **
SJC	5.5(4.3)	5.1.(3.6)	NS	0.6 (1.7)	1.2(1.5)	NS
TJC	8.1(5.3)	7.2(6.0)	NS	0.8 (2.3)	1.6(2.8)	NS
PGA	52.4(22.9)	50.0(16.3)	NS	15.5(17.4)	27.3(18.7)	0.013
ESR	41.7(25.4)	41.2(28.2)	NS	50.5(34.7)	24.4(15.2)	<0.0001
CRP	37.1(40.1)	34.2(44.9)	NS	12.3(12.0)	13.4(12.9)	NS
DAS28- ESR	5.2 (1.3)	5.1(1.1)	NS	2.9 (0.9)	3.1(1.0)	NS
DAS28- CRP	4.9 (1.1)	4.7(1.0)	NS	2.2 (0.8)	2.8(1.0)	0.06

*T₀HIV vs. T₀Control; ** T_LHIV vs. T_L Control; T₀ = Time of initial RA diagnosis; T_L = Time of last clinic visit; SJC = Swollen joint count; TJC = Tender joint count; PGA = Patient global assessment; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease activity score 28 joint count; NS = Not significant.

Table 3.6 DAS28-CRP comparison between the HIV and control group with respect to disease activity categories

DAS28-CRP scores	T ₀ Number of patients (%)			T _L Number of patients (%)		
	HIV group	Control group	p value	HIV group	Control group	p value
≥ 5.1	20 (46.5)	14 (32.5)	NS	2 (4.6)	1 (2.3)	-
≥3.2 – < 5.1	14 (32.5)	23 (53.4)	NS	4 (9.3)	12 (28)	NS
>2.6 – < 3.2	1 (2.3)	2 (4.6)	-	3 (7)	7 (16.2)	NS
≤ 2.6	2 (4.6)	0	-	32 (74.4)	23 (53.4)	NS

T₀ = Time of initial RA diagnosis; T_L = Time of last clinic visit; DAS28 = Disease activity score 28 joint count; NS = Not significant.

Table 3.7 DAS28-ESR comparison between the HIV and control group with respect to disease activity categories

DAS28-ESR scores	T ₀ Number of patients (%)			T _L Number of patients (%)		
	HIV group	Control group	p value	HIV group	Control group	p value
≥5.1	26 (60)	20 (46.5)	NS	3 (7)	2 (4.6)	NS
≥3.2 – <5.1	11 (25.6)	21 (48.8)	NS	14 (32.5)	13 (30.2)	NS
>2.6 – < 3.2	2 (4.6)	1 (2.3)	-	13 (30)	11 (25.6)	NS
≤ 2.6	2 (4.6)	1 (2.3)	NS	11 (25.6)	17 (39.5)	NS

T₀ = Time of initial RA diagnosis; T_L = Time of last clinic visit; DAS28 = Disease activity score 28 joint count; NS = Not significant.

Table 3.8 Comparison of MTX treated patients between groups at different time points

	HIV Group Number of patients (%)			Control Group Number of patients (%)		p Value		
	T ₀	T _H	T _L	T ₀	T _L	*	**	***
MTX	20 (46.5)	34 (79)	5 (11.6)	19 (44.2)	36 (83.7)	NS	NS	0.0002

*T₀ HIV vs. T₀ Control; ** T_H HIV vs. T_L Control; ***T_L HIV vs. T_L Control; T₀ = Time of initial RA diagnosis; T_H = Time when HIV diagnosis made; T_L = Time of last clinic visit; NS = Not significant; MTX = Methotrexate.

CHAPTER 4: DISCUSSION

In this present study, of the 1712 RA patients, 85 were HIV positive reflecting a prevalence of 4.9% HIV infection in this group, which is similar to the 5% HIV burden reported to affect the sub-Saharan adult population (UNAIDS, 2010). The RA disease activity improved after HIV seroconversion, and the DAS28-ESR proved to be a less reliable measure of disease activity because of the non-specific increase in ESR. As discussed earlier, previous case reports have reported various outcomes, but this study has shown significant overall clinical improvement in disease activity.

The female to male ratio in the HIV positive group of 9:1 is much higher than the 5:1 reported previously in RA in this population. These findings again highlight the burden of HIV being disproportionately higher in South African females as shown previously in the general population (Rehle et al., 2010). Both the HIV and control groups had a mean age on RA disease onset under the age of 40. This is in keeping with previous studies in the developing world, including Africa, and is thought to be related to an overall lower life expectancy (Kalla and Tikly, 2003, Tikly et al., 2003).

The HIV and control groups were matched for age and sex, and had similar disease activity at initial presentation, the vast majority of whom had moderate to high disease activity. These findings are consistent with recent studies in the same population and other Sub-Saharan African populations (Mody and Meyers, 1989, Ndongo et al., 2009), showing that patients attending the Chris Hani Baragwanath

Academic Hospital frequently have severe disease (Hodkinson et al., 2011). This is at odds with earlier studies in other parts of sub-Saharan Africa, where RA is considered to run a mild course (Adebajo and Reid, 1991).

On follow-up, both the HIV and control groups improved with treatment. Despite the fact only a minority of patients in the HIV group were on MTX at last visit (11.6 % vs. 83.7% in the control group, $p=0.0002$), the HIV group fared significantly better with respect to the PGA and a trend towards lower overall disease activity, as measured by the DAS28-CRP. A higher proportion of patients in the HIV group achieved disease remission compared to the control group (74.4% vs. 53.4%), although the difference again was not statistically significant. These findings are consistent with the earlier anecdotal reports of RA disease activity declining with HIV infection (Bijlsma et al., 1988, Calabrese et al., 1989, Lapadula et al., 1997).

It is not clear from the present study, what the mechanism is for the improvement in disease activity in the HIV group. Although the CD4 count was low in the HIV patients in whom it was taken, there was no clear relationship between the CD4 count and the decline in disease activity. Moreover, there was no further significant decline in the CD4 count between T_H to T_L , although disease activity declined significantly during that period. Previous studies targeting CD4 T-lymphocytes have shown only modest improvement in disease activity (Scheerens et al., 2011). The pathophysiology of RA and HIV is complicated and why some patients have ongoing joint inflammation

despite being immuno-suppressed, supports work regarding independent T-lymphocyte functioning (Bartok and Firestein, 2010). Conversely, no significant increase in disease activity was noted in the 6 patients who were started on HAART. However, there have been isolated case reports of RA disease flares occurring on commencing HAART, possibly as part of an immune reconstitution (Azeroual et al., 2008, Ornstein et al., 1995).

Although the vast majority of patients in the HIV group did well, a small proportion continued to have moderate to high disease activity at T_L , based on the DAS28-CRP. Given that MTX affects both T cell numbers and function (Hoshida et al., 2007) and in its own right results in infections like pneumocystis pneumonia, a common occurrence with HIV infection, the safety of MTX, as the “anchor” drug for RA needs to be systematically investigated in HIV patients with RA.

Another important observation in the present study was that in spite of improvement in all clinical parameters and the CRP following HIV seroconversion, the ESR showed no change. In fact, the mean ESR was numerically higher at T_L compared to T_0 , but this did not reach statistical significance. This had a direct impact on DAS28-ESR, such that at T_0 there was no statistical difference between the DAS28-CRP and DAS28-ESR, but the mean DAS28-ESR being significantly higher than the DAS28-CRP at both T_H and T_L . Compared to the DAS28-CRP, the DAS28-ESR overestimated disease by more than 30%. These findings suggest that in patients

with HIV and RA, the DAS28-ESR is not a reliable measure of overall disease activity.

The mechanism behind an elevated ESR probably stems from the hypergammaglobulinemia (Ndakotsu et al., 2009). With the decrease in number of CD4 cells, comes with it a shift to anti-inflammatory cytokines, IL-4 and IL-10, which up regulate humoral immunity and the production of immunoglobulins. The non-specific hypergammaglobulinemia is caused by increases of IgA, IgM and beta 2-microglobulin (Schwartlander et al., 1993) and this results in an elevated ESR value which has been shown to be predictive of HIV status (Modjarrad et al., 2005). The ESR is also influenced by other factors such as plasma proteins, age, sex, rheumatoid factor, and anaemia (Talstad et al., 1983). These may all lead to an elevated ESR value, thereby overestimating DAS28-ESR score and overall RA disease activity. CRP seems less effected by the above mentioned factors and has been proven to reflect more short-term disease activity changes, where as ESR reflects activity over a longer period. A longitudinal study from Japan comparing DAS28-ESR to DAS28-CRP showed that the latter underestimates disease activity compared to the former (Matsui et al., 2007). But in the setting of HIV, Schleicher et al also found that the clinical utility of ESR in the diagnosis of co-infections, such as tuberculosis or *Streptococcus pneumoniae*, was poor compared to the CRP because of the non-specific elevation of ESR (Schleicher et al., 2005).

As with any retrospective studies there are potentially numerous limitations that need to be taken into consideration. There was incomplete patient clerking notes leading to missing data at some time points. Better control group selection matched for not only age and sex, but disease duration as well, would have strengthened the data. The incomplete data with respect to the CD4 count and HIV viral load meant that it was not possible to analyse the relationship of these parameters with disease remission. A critical component in the DAS scores is the tender and swollen joint counts and it is well known that there is inter-observer variability among different physicians, which also needs to be taken into consideration (Grunke et al., 2010). Too few of our patients were on HAART to give a comment on disease activity response to improving immune status.

CHAPTER 5: CONCLUSION

Up until the end of 2008, there was a 4.9 % incidence of HIV amongst the RA patients in the Rheumatology Unit at Chris Hani Baragwanath Academic Hospital. Among patients who contracted HIV infection after the diagnosis of RA, disease activity overall improved with HIV seroconversion, which was sustained in the absence of MTX treatment. In spite of the overall improvement in disease activity, there remains an unmet need with respect to the safety of DMARD therapy in HIV patients with ongoing disease activity. The DAS28-ESR is a less reliable measure of disease activity than the DAS28-CRP because of the non-specific increase in ESR with HIV infection.

Further work is needed on 1) relationships of the CD4 cell count and viral load to RA disease activity; 2) effect of HAART on disease activity in RA; 3) safety of DMARDs and HIV infection and; 4) predictors of RA remission in HIV patients.

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APPENDIX A

Data collection sheet

Patient Initials: _____ Patient Age: _____ Sex: _____ Smoker: _____
Study No: _____

Age of onset of RA _____ Disease duration of RA _____ (Till 31/12/08)

Age of diagnosis of HIV _____

Duration of HIV since diagnosis: _____

Use of ARV's: Yes / No _____ Duration of ARV: _____

<u>Variable</u>	<u>At Presentation</u>	<u>At/Closeset to HIV Diagnosis</u>	<u>At last visit</u>
Tender joint count			
Swollen joint count			
Patient's global assessment			
ESR			
CRP			
Functional Class			
Nodules			
Viral load			
CD4 count			
Rheumatoid factor			
Anti-nuclear factor			
Anti CCP antibody			
Choroquine			
SASPEN(Dose)			
MTX(Dose)			
Arava(Dose)			
Prednisone(Dose)			

Ever TB treatment: Y / N _____ Number of treatments: _____ ?Before / After RA Diagnosis
? Before / After HIV Diagnosis

TB Diagnosis- Pulmonary

-Suggestive CXR.

-Sputum.

-Extrapulmonary- LN FNA.

-BMAT.

-Synovial aspiration.

-Synovial biopsy.

-Other _____

Other serious infection/ malignancy: _____

Zoster : Yes / No -?Before / After RA Diagnosis -? Before / After HIV Diagnosis

APPENDIX B

Ethics certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

R14/49 Dr Gareth Scott

CLEARANCE CERTIFICATE

M090814

PROJECT

Human Immunodeficiency Syndrome and
Rheumatoid Arthritis

INVESTIGATORS

Dr Gareth Scott.

DEPARTMENT

Internal Medicine/Rheumatology

DATE CONSIDERED

09.08.28

DECISION OF THE COMMITTEE*

Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE

30.08.09

CHAIRPERSON



(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof M Tikly

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

