AN ANALYSIS OF CLINICAL SIGNS AND SYMPTOMS WHICH BEST PREDICT THE NEED FOR HAART INITIATION IN HIV INFECTED SOUTH AFRICAN WOMEN

AN ANALYSIS OF CLINICAL SIGNS AND SYMPTOMS WHICH BEST PREDICT THE NEED FOR HAART INITIATION IN HIV INFECTED SOUTH AFRICAN WOMEN

By

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the degree of

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In Wits medical School, The Faculty of Health Sciences, University of The Witwatersrand

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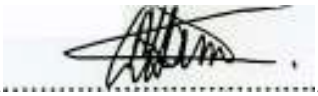
Declaration

I, Dr. PIUS GERALD HORUMPENDE, hereby declare that this research report is my own original work. It is submitted for the award of the degree of Master of Science in Medicine (MSc Med) in the field of Epidemiology and Biostatistics of the University of the Witwatersrand, Johannesburg-South Africa. It has not been submitted before for any other degree award or examination at this or any other University.

Signature…….  ……

Dr. PIUS GERALD HORUMPENDE

Date……15th January…….. 2010.

Dedications

To my Family with Love: Dr. Edna my wife and J. R. Kanyange my daughter who have endured a lot in my absence for studies in The Republic of South Africa.

To my sister: Felister Irandagiye Horumpende (RIP) (1963-2006) who acquired HIV in marriage and died of AIDS on 28th August 2006 at 16.00 hours in Tanzania.

To Dr. Julius Kambarage Nyerere (RIP) (1922-1999) who made sure, unlike other African Presidents, that even children of poor peasants in Tanzania go to school.

Abstract

Background. South Africa is currently experiencing one of the most severe AIDS epidemics in the world. The major challenge lies in prompt identification and early initiation of treatment in those eligible for HAART. Clinical staging has previously been recommended for use in settings where CD4 + count testing is not available. We conducted secondary data analysis to determine whether clinical symptoms and signs are useful in predicting the need for HAART initiation (CD4 + count < 200 cells/μL) in South Africa.

Methods. Screening data from a randomized controlled trial in women who were HIV positive were analysed. All participants were interviewed using a structured questionnaire to elicit symptom history and then physical examination was done. Participants were staged using WHO criteria. Blood was drawn for CD4 + testing. The association between signs and symptoms and a CD4 + < 200 cells/μL was assessed using logistic regression.

Results. Among 589 HIV infected women aged between 18 and 58 years, 90% were assessed as WHO clinical stages I/II. The median CD4 + count was 403 cells/μL (IQR: 273-586). Among women who were WHO stage I/II, 13% had CD4 + count < 200 cells/μL and required HAART. The WHO clinical staging had a low sensitivity (4%) but high specificity for detecting those that require treatment.

Conclusion: In a setting where asymptomatic patients are diagnosed with HIV, clinical assessment can not replace CD4 + count testing as a method of identifying those that need treatment.

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Le fléau n'est pas à la mesure de l'homme, on se dit donc que le fléau est irréel, c'est un mauvais rêve qui va passer. Mais il ne passe pas toujours et, de mauvais rêve en mauvais rêve, ce sont les hommes qui passent, et les humanistes en premier lieu, parce qu'ils n'ont pas pris leurs précautions.

(A pestilence isn't a thing made to man's measure; therefore we tell ourselves that pestilence is a mere bogey of the mind,a bad dream that will pass away. But it doesn't always pass away, and from one bad dream to another, it is men who passaway, and the humanists first of all, because they haven't taken their precautions.)

Albert Camus, La Peste, 1947

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List of Abbreviations

AIDS…….....Acquired Immune Deficiency Syndrome

ART…….....Antiretroviral Therapy

ASSA……...Actuarial Society of South Africa

CD 4+ Cells…….....Cluster of Differentiation type four protein (Cells responsible for body immunity and defence against diseases)

CDC…….....Centres for Disease Control

DOH……..……...Department of Health

HAART……...Highly active Antiretroviral Therapy

HIV…….……...Human Immunodeficiency Virus

HREC……..…Human Subjects Research Ethics Committee

IVDU……..……..Intravenous Drug Users

KS…….…….Kaposi's Sarcoma

NGO……..……Non- Governmental Organization

PPE……..……...Pruritic Papular Eruption

PTB……..……...….Pulmonary Tuberculosis

RHRU…….....Reproductive Health and HIV Research Unit

TLC…….……...…Total Lymphocyte Count

UNAIDS……..……Joint United Nations Action against AIDS

UNICEF……..……..…United Nations Children's Fund

WHO……..…….World Health Organization

BMI.....Body mass Index

CI……...Confidence Intervals

IQR……..…….Interquartile Range

Chapter 1: Introduction and Literature Review

1.0 Introduction and Background

1.1 Historical rationale for WHO clinical staging

The World Health Organization (WHO) AIDS surveillance case definition was first developed by WHO in October 1985 in Bangui, Central African Republic. It was then revised in 1994 after a heavy criticism to incorporate the statement that HIV testing should be done. The AIDS case definition, and subsequent WHO clinical staging systems, have been proposed to be used in poor-resourced countries where laboratory facilities to test for CD4 + count are inaccessible (Grant, 2001).

The second revision of the WHO clinical staging system was in 2005.The WHO classification of HIV- associated clinical disease was revised in order to provide greater consistency between the adult and paediatric classification systems. Revisions were meant to form part of the baseline assessment (first visit) on entry into a care and treatment program and used to guide decisions on whether to start co-trimoxazole prophylaxis and when to start and switch ART in situations where CD4 + testing is not available (WHO,2006)

The WHO clinical staging system for HIV/AIDS, as developed in 1990, emphasized the use of clinical parameters to guide clinical decision-making for the management of HIV/AIDS patients. The WHO clinical staging system is needed for use in resource-limited settings where there is a limited access to laboratory services. The system has been widely used in resource-limited countries, particularly in the African Region (WHO, 2005). Several studies (Torpey, 2009; Jaffar, 2008; Edathodu, 2007; Erkose, 2007; Kagaayi, 2007; McGrath, 2007) have evaluated the correlation between CD4 + count and WHO staging in Africa. Three recent

studies (Torpey, 2009; Jaffar et al, 2008; McGrath, 2007) have indicated that the WHO clinical staging system is inadequate in correctly identifying individuals eligible for HAART initiation. The three studies suggested that CD4 + measurement is actually a much more accurate means to predict disease progression and hence the indication for HAART initiation as HAART became available.

1.2 Global overview of HIV/AIDS

An estimated 39 – 65 million people in the world were living with HIV/AIDS in 2007 (UNAIDS, 2008). Approximately 96% of HIV/AIDS patients live in low and middle income countries, with sub-Saharan Africa being the region worst affected. Even though sub-Saharan Africa is home to only 10 % of the world's population, 67% of all patients who are HIV positive reside here (UNAIDS, 2008).

While most of the 40 million people living with HIV/AIDS at the end of 2006 were in low- and middle-income countries, 20% of those in need of treatment were receiving highly active antiretroviral therapy (HAART) (UNAIDS, 2006).

Guidelines developed by the WHO for the use of HAART in low-income countries state that HIV– infected individuals should commence HAART if they have WHO stage IV disease, stage III disease and a CD4 + T lymphocyte cell counts of ≥ 350 cells/μL, or stages I or II disease with CD4 + cell count < 200 cells/μL (WHO, 2006). Recently WHO has recommended increasing this threshold for stages I and II individuals to 350 cells/μL (Brodt, 2009). In many parts of sub-Saharan Africa, facilities for laboratory diagnosis and monitoring of CD4 + count are limited and inadequate to sustain the escalating of the HIV/AIDS epidemic (Jaffer, 2008). In resource-constrained settings, the cost of laboratory investigations is a key constraint that affects the initiation and monitoring of HAART (Torpey, 2009).

This study is undertaken to determine whether the use of clinical symptoms and signs alone is feasible and appropriate in asymptomatic individuals in a South African setting and hence in any high burden HIV setting especially in sub – Africa where laboratory diagnostic capacities are limited.

1.3 Problem Statement

CD4+ T lymphocyte count decline is an important predictor of progression to AIDS. In the developed world, this parameter is used to identify patients who need prophylaxis for opportunistic infections and HAART. In countries with limited resources, despite the increased access to HAART, CD4+ count testing is often not available (Lynen, 2006). While CD4+ count is the best indicator for the need to commence treatment, CD4 + count determination is not feasible in settings with poor access to laboratory services or where demand for services is high. Barriers to initiation of appropriate antiretroviral treatment include lack of CD4+ count measurements in the laboratory and trained personnel to make accurate clinical staging of HIV (Costello, 2004;UNAIDS/WHO,2006). In these instances, it may be useful to identify those that need treatment at the time of their diagnosis. The performance of WHO staging is questionable (Torpey, 2009). It is also not clear how the WHO staging works in HIV + population in good health. There is increasing pressure to initiate treatment early (Brodt, 2009). Thus a need arises, therefore, to determine whether the use of clinical signs and symptoms alone is feasible and appropriate in a South African setting.

1.4 Literature review

1.4.1 Prevalence of HIV in South Africa

South Africa is one of the worst affected countries in the world by the HIV pandemic (Steinbrook, 2004). By the end of 2008, 5.2 million of the 48 million people were living with HIV in South Africa (HSRC, 2009), and almost 1,000 AIDS deaths occurring every day (UNAIDS/WHO, 2008). HIV prevalence among pregnant women has risen steadily from 10.4 % in 1995 to 30.2 % (95% CI 29.1-31.2) in 2005. In the 2008 HSRC survey, amongst the general population, HIV prevalence was 10.6% (12.8% in females and 9.5% in males).

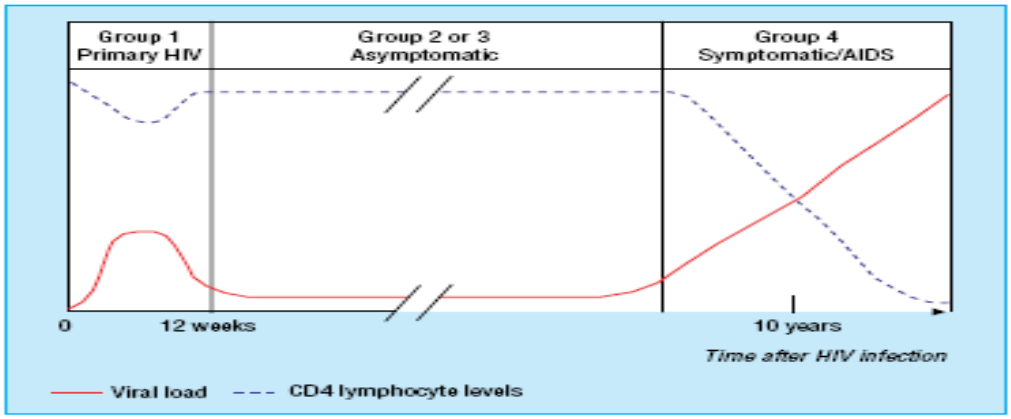
Women are at a higher risk of HIV infection than men in South Africa.

Evidence shows that women are at a higher risk of HIV infection than men. The South African National HIV prevalence, incidence, behaviour and communication survey conducted in 2008 showed that females aged 15-19 years have an 2.7 times higher HIV prevalence than males (6.7% compared to 2.5%) and account for 83% of the recent HIV infections in this age group. In African adults aged 15-49 years the HIV prevalence was 16.9%.The figure for African women in the same age group is 24.4% (Shisana, 2009).Young women are particularly affected. A cross-sectional, nationally representative, household survey was done in South Africa among 11, 904 young people in the age group 15 - 24 year olds. The results showed that young women were significantly more likely to be infected with HIV in comparison with young men (15.5% versus 4.8%) (Pettifor, 2005).

Natural history of HIV infection

In sub-Saharan Africa, the major route of HIV transmission is heterosexual in about 90% of cases. Initial infection with HIV is sub-clinical. This is followed by an asymptomatic phase lasting a median duration of 10 years (Jaffar, 2004). Early symptomatic infections include fever, unexplained weight loss, recurrent diarrhoea, fatigue and headache. Subsequent manifestations include cutaneous or dermatological conditions. Late symptomatic stage begins as the CD4 + count falls to lower than 200 cells/µL and the risk of developing AIDS-related opportunistic infections or malignancy increases (Mindel, 2001) (Fig.1.1).

Figure 1.1 Schematic Natural History of HIV infection



Association between virological, immunological, and clinical events and time course of HIV infection

(Source: Mindel, 2001)

There are few studies on the natural history of HIV infection among African populations, and little is known about the natural history of HIV infection in Africa. However, in a review, Jaffar (2004) showed that the time from infection to symptomatic (AIDS) phases was similar for sub Saharan African patients when compared to patients in developed countries prior to introduction of HAART. The authors noted that there was a more rapid progression from

symptomatic phase to death among sub-Saharan African cohorts than those of developed countries. The rapid progression was attributable to the background co-morbidities in among the patients from sub Saharan Africa notably tuberculosis, sexually transmitted infections, clinical malaria, and high malaria parasitaemia. The co-morbidities were coupled with a lack of treatment of these potentially curable infections due to poor clinical services (Jaffar, 2004).

1.4.2 A need for HAART to treat opportunistic infections and prolong life

HAART is currently recommended for at a CD4 + count < 200 cells per μL in South Africa (DOH, 2006). However, a recent computer simulation model of HIV disease has indicated that initiating HAART at a CD4 + count threshold of 350 cells per μL would remain cost-effective over the next 5 years before the results of clinical trials to determine the most plausible CD4 + count threshold for HAART initiation (Walensky, 2009). Treatment is started at this level in order to prevent opportunistic infections and death. With increased use of HAART the survival among even the advanced HIV disease patients has improved substantially (Mindel, 2001; Munderi, 2004; Castilla, 2005 and Louwagie, 2007). A study from Cape Town showed that delay in the initiation of treatment lead to the increase of mortality and morbidity (Lawn, 2006).

The best possible time to begin HAART has recently been established to be CD4 + count ≥ 350 cells per μL where 18 cohort studies of patients with HIV were analysed (Brodt, 2009). However Wood et al, (2005) had described data from observational studies suggesting a longer term benefit when HAART is begun well before the CD 4 + count falls to 200 cells/μL or less. An analysis of data from 10, 885 individuals who were AIDS free and ART-naive at onset of HAART found that the risk of progression to AIDS was higher in those starting HAART at

CD4 + count 200 cells/µL or less (HR=3·30, 95% CI: 2·51–4·33) compared to those with CD4 + count 201–350 cells/µL, (HR=1·46, 95% CI: 0·96–2·21) or 351–500 cells/µL after adjusting for lead-time bias and hidden events (Sterne , 2006). Further evidence of goals and importance of HAART is to prevent opportunistic infections, resistance to HAART and also to prevent the occurrence of non AIDS events (SMART trial, 2006).

Two studies underscored other benefits of early initiation of HIV treatment. These benefits include potential effectiveness in reducing HIV secondary transmission (Castilla, 2005) and preservation of ability to use chemokine receptor CCR 5 entry inhibitors (Deeks, 2006).

There is also strong evidence for the clinical benefit of HAART in adults with advanced HIV/AIDS as determined virologically, clinically and immunologically (WHO/HIV/2005).

Munderi et al, (2004) conducted the Development of Anti-Retroviral Therapy in Africa trial on the CD4 + response to HAART in previously untreated adults with HIV infection in Africa. This trial was an open-label, randomized trial comparing 2 therapeutic approaches to be tested in resource-poor settings. Participants were 3,000 symptomatic ART-naive adults from 3 sites (2 in Uganda, 1 in Zimbabwe) who had CD4 + < 200 cells/µL who received 3-drug HAART, and were followed for 5 years. The trial showed an increase in CD4 + count (immunological response) whereby 49 % adults had an increase in CD4 + count by at least 100 cells/µL at 24 weeks (median increase 98, IQR: 44-152).The trial concluded that achieving CD4 + count increases of > 100 cells after 24 weeks on HAART in Africa appears to occur regardless of pre-HAART factors including low baseline CD 4+ count.

Munderi et al (2004) again showed the benefit of HAART among the participants in Entebbe cohort. The Entebbe cohort (EC) is an active, community-based clinical cohort of HIV-infected adults set up in 1995.The death rate observed in patients with CD4 + < 200 cells/µL at

enrolment into the EC during the first year (1995/96) was compared with the rate observed in the DART study during the first year of follow-up. The study showed that the introduction of HAART resulted in a highly statistically significant reduction in HIV related mortality among patients with advanced HIV infection in this Ugandan community. These data also showed that HAART initiation even in those most severely immunosupressed (CD4+ < 50 cells/μL) was still highly beneficial.

1.4.3 Treatment needs assessment in South Africa

An estimated 1,720,000 HIV infected people in South Africa require treatment as ascertained by a recent study using a Markov model of HIV progression in adults, combined with estimates of annual new HIV infections from a national AIDS and demographic model. (Johnson, 2009).Those accessing HAART from the public and NGO sectors by the end of 2005 were 200,000 people only (Nicoli,2006).

Table 1.1 An estimated number of people in need of HAART in South Africa, Malawi, Mozambique and Swaziland.

	South Africa	**Malawi**	**Mozambique**	**Swaziland**
Total population	49 200 000	11 200 000	18 000 000	1 029 000
Mean adult HIV seroprevalence	10.6%	15%	14%	38%
Total number of HIV-positive people	5 215 200	900 000	1 400 000	200 000
Estimated number of people in need of HAART	1 72 1212	170 000	270 000	20 000

{Source: Johnson, 2009}

There are several reasons why treatment uptake is low. Low counselling and testing rates may be attributed to fear of knowing one's status and fear of disclosure which may lower treatment uptake (Newman, 2007). Lack of laboratory diagnostic services in sub- Saharan Africa is an impediment to accurate diagnosis and hence initializing treatment (Petti, 2006). In one publication, Erhabor (2006) has shown that the absence of CD4 + count measurements is a barrier to the decision to initiate HAART among HIV infected Nigerians.

1.4.4 The value of clinical staging in the decision to initiate treatment

The WHO proposed a staging system in 1994 to assist poorly - resourced countries for surveillance and monitoring of HIV disease. Staging is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and does not require a CD4+ cell count. It is a symptom based classification. This staging system is used in many countries to determine eligibility for antiretroviral therapy. Clinical stages are categorized as I through IV, progressing from primary HIV infection to advanced HIV/AIDS. These stages are defined by specific clinical conditions. For the purpose of the WHO staging system, adolescents and adults are defined as individuals aged $\geq$ 15 years (WHO, 2005).

Table 1.2 The WHO Clinical Staging criteria for HIV/AIDS

REVISED WHO CLINICAL STAGING OF HIV/AIDS
FOR ADULTS AND ADOLESCENTS

(Interim African Region version for persons aged 15 years or more with positive HIV antibody test or other laboratory evidence of HIV infection)[b]

TABLE 1. REVISED WHO CLINICAL STAGING OF HIV/AIDS FOR ADULTS AND ADOLESCENTS

Primary HIV infection

- Asymptomatic
- Acute retroviral syndrome

Clinical stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)

Clinical stage 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulcerations
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections of fingers

Clinical stage 3

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

- Severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Conditions where confirmatory diagnostic testing is necessary

- Unexplained anaemia (<8 g/dl), and or neutropenia (<500/mm^3) and or thrombocytopenia (<50 000/ mm^3) for more than one month

[b] All clinical events or conditions referred to are described in the Annexes. The UN defines adolescents as persons aged 10–19 years but, in the present document, the category of adults and adolescents comprises people aged 15 years and over for surveillance purposes.

Clinical stage 4

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Oesophageal candidiasis
- Extrapulmonary TB
- Kaposi's sarcoma
- Central nervous system (CNS) toxoplasmosis
- HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary:

- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy (PML)
- Candida of trachea, bronchi or lungs
- Cryptosporidiosis
- Isosporiasis
- Visceral herpes simplex infection
- Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
- Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)
- Recurrent non-typhoidal salmonella septicaemia
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Visceral leishmaniasis

Source: WHO/HIV/2005.02

Several studies have been done to validate the WHO clinical staging. The majority of the studies have suggested that a simple rearrangement of the symptoms and signs in a given environment could better predict the eligibility of patients in poorly resourced settings (Malamba, 1999). Table 1.2 summarises data from 14 studies which address different aspects of validation of WHO clinical staging in predicting eligibility for HAART. The studies assess

the relationship between clinical symptoms and signs and either WHO stage, CD4 + count and/ or risk of progression to AIDS.

In a routine service delivery setting in Uganda, Jaffar et al (2008) assessed the ability of the WHO clinical staging to accurately identify HIV-infected patients in whom HAART should be started. Among 4302 patients, the sensitivity of the WHO criteria to identify eligible patients for HAART i.e. CD4 + count < 200 cells/ µL was 52% (95% CI: 50-54). In this setting, a large number of individuals (about 50%) would not have received treatment if eligibility to HAART was assessed on the basis of WHO clinical staging alone. These data suggest that in settings where clinical staging alone is used, many patients would have had treatment deferred until a time when they have much more advanced disease.

One author suggested a targeted CD4 + testing only to certain HIV infected individuals in WHO stage III whose staging is based on weight loss alone in settings where routine CD4 + count is not feasible due to poor resources (Lynen et al 2006).

In another study (Kagaayi, 2007) the ability of WHO clinical staging to predict CD4 + cell counts of 200 cells/µL or less was evaluated among 1,221 patients screened for HAART. The sensitivity and specificity of WHO criteria was 51% and 88% respectively. Clinical criteria missed half the patients with CD4 + cell counts of 200 cells/µL or less.

Other authors highlighted the importance of CD 4+ cell measurements for the scale-up of ART provision in resource-limited settings (Kagaayi et al, 2007; Jaffar et al, 2008).

From the literature reviewed the majority of studies recommended modifications to WHO staging by a simple rearrangement of the symptoms and signs in order to accurately predict eligibility for HAART initiation in their respective populations (Malamba, 1999; Morpeth, 2007).

Table 1.3 Studies analyzing clinical symptoms and signs to predict the need to initiate HAART.

Author and study area	Year	Design	Study Population	Clinical Symptoms and signs	Results	Outcome Measure	Comment
(1)TorpeyK,et al (Zambia) AFRICA	2009	Retrospective study	5784 HIV patients		-29.5% were in stages I and II and had a CD 4 ≤ 200 cells/μL 34.6 had a CD 4 count ≤ 350 cells/μL and were in WHO stages I/ II.	Sensitivity, Specificity NPV,PPV	WHO Clinical staging is inadequate to identify persons eligible for HAART
(2) Jaffar et al (Uganda) AFRICA	2008	A pragmatic effectiveness study	4302 subjects screened for ART		-About 50% with WHO stage I/II had CD 4 count < cells/μL -the sensitivity and specificity (95% CI) of WHO stage III/IV against a CD4 count < 200 x 10^6/l were 52% (50, 54%) and 68% (66, 70%) respectively.	Sensitivity and specificity	WHO clinical staging missed 50% of patients eligible for ART. -Urgent need for greater CD4 count prior to initiation of ART to accompany the roll-out of ART.
(3) Kagaayi et al (Uganda) AFRICA	2007	Cohort Study	1221 patients of whom 65% were women		Sensitivity was 51% , Specificity was 88%, the positive predictive value was 64%, the negative predictive value was 81%	Sensitivity, Specificity, Positive predictive value, Negative predictive value, WHO staging	Clinical criteria missed half the patients with CD4 cell counts of 200 cells/μl or less, highlighting the importance of CD4 cell measurements for the scale-up of ART provision in resource-limited settings.
(4) Erkose and Erturan (Turkey) EUROPE	2007	Cross Sectional	64 HIV infected out patients coming for viral load and CD 4+ count measurements	Oral candidiasis	No correlation between oral candida and declining CD 4 +count.	CD 4+ counts	High prevalence of candida among HIV infected patients but not indicative of declining CD 4 +count.

(5) McGrath (Malawi) AFRICA	2007	Cross sectional	11,800 HIV seropositive adults aged 18-59 years in selected households in Karonga DSS site.		-WHO staging had a sensitivity 50% and specificity 96% in predicting those eligible for HAART -Those eligible for HAART by WHO criteria were 31% and by CD 4 count criteria they were 38%	Sensitivity and specificity	WHO clinical staging alone missed 2/3 i.e. two thirds of those eligible for ART by clinical staging and CD 4 count
(6) Morpeth S. (Tanzania) AFRICA	2007	Cross sectional	202 HIV infected adult patients	Mucocutaneous Manifestations	The feature most strongly associated with CD4 count <200 (p-value <0.0001) was the presence of mucocutaneous manifestations (72%), with a sensitivity of 85% and specificity of 63% for predicting CD4 count <200 cells/μL	Symptoms & signs,CD 4 counts & Laboratory parameters(TLC and ESR)	The presence of mucocutaneous manifestations was a strong predictor of CD4 count <200 cells/μL and enhanced the sensitivity of the 2006 WHO staging criteria for identifying patients likely to benefit from antiretrovirals.
(7) Edathodu J(Saudi Arabia) ASIA	2007	Retrospective chart review	191 HIV infected patients	Clinical events listed in the 2005 WHO staging	16/110 (15%) in WHO stage I had CD4<200; 3/10(30%) in WHO stage II had CD4 + count <200 and 10-15% of patients at stages III and IV had CD4 count >350.	WHO clinical staging and CD4 + counts	WHO clinical staging criteria missed 19/191 i.e. 10% of those eligible for HAART
(8) Lynen et al.(Cambodia) ASIA	2006	Retrospective analysis of cohort data	648 HIV patients in a follow up at the Sihanouk Hospital		9 % i.e.52 patients were wrongly identified by WHO criteria to be in need of HAART(i.e. had CD4 + count >200)	sensitivity, specificity, and accuracy of the 2003 WHO criteria to start HAART	Target CD 4 testing to patients in WHO stage 3 whose staging is based on weight loss alone.
(9) Teck et al (Malawi) AFRICA	2005	Cross sectional	457 HIV positive individuals in stages 3 and 4 registered at HIV clinic	TB	413/457 i.e. 90% of Patients in WHO stage 3 and 4 had CD4 + count ≤350 cells/μL while 10 % had CD 4 count > 350 cells/μL.	CD 4+ counts	(1) 10 % would be started on ART prematurely.(2) WHO staging is an appropriate method to predict ART eligibility (especially in advanced stages) (3) Active or previous TB patients in stages 3 and 4 had low CD4 + count (<350) thus eligible for ART.
(10) Costello et al (Thailand)	2004	Cross	839 HIV positive		The WHO guidelines had a sensitivity of 34.1% in men and 31.8% in women	Sensitivity and	WHO staging was improved by a

ASIA		sectional	Blood donors		to detect persons with CD4 + count < 200	specificity	combination of anaemia
(11) Muhammad B et al (Tanzania) AFRICA	2003	A sub-study from an ongoing cohort study	716 Police Officers of whom 127 were HIV positive	Fungal infections, herpes zoster, Pruritic papular eruption, seborrheic dermatitis and Kaposi's sarcoma	Mean CD4+ counts (percentage) : KS: 75. Cells/µL (4.0%) PPE: 71. cells/µL	CD 4 counts	Pruritic Papular Eruption (PPE) i.e. skin rash; and Kaposis Sarcoma (KS) are markers of severe immunodeficiency due to HIV.
(12) Malamba SS et al (Uganda) AFRICA	1999	A Cohort Study	1666 Incident and prevalent HIV cases followed up for 7 years (1990-1997).	Unexplained prolonged fever ,severe bacterial infection ,HSV ,cryptosporidiosis and Oral candidiasis	(1)Unexplained prolonged fever and severe bacterial infection had survival probabilities closer to stage II conditions; (2) HSV > 1 month and cryptosporidiosis with diarrhoea had survival probability closer to stage III conditions; (3) Oral candidiasis was closer stage IV conditions.	WHO clinical staging	-WHO staging is useful to predict low immunity (low CD4 + cells) and Survival even without the laboratory markers. -A simple re-arrangement of a few clinical conditions will improve prediction of Low CD4 + and thus prognosis by the WHO system.
(13) Kassa et al (Ethiopia) AFRICA	1999	Cross sectional	86 HIV positive individuals in all WHO stages	Minor weight loss, pulmonary tuberculosis	23/86(27%) had CD 4 count < 200 cells/µL BUT only one (1) individual was in WHO stage IV.	CD4 + counts, viral load, sensitivity and PPV and WHO staging	-Clinical staging missed 27% eligible for ART; -Overall good correlation between WHO staging and CD 4 count.
(14) Aylward RB et al (Baltimore) USA	1993	Cross sectional	694 HIV seropositive IV Drug Users		The risk of progression to AIDS was increased in those in WHO stages 2 (HR 1.51 CI: 0.6-3.8) and 3(HR 2.39 CI: 1.4-4.1) compared to those in WHO stage 1.	The hazard for progression to AIDS	This study supports the utility of the WHO staging system in predicting progression from HIV seropositivity to AIDS on the basis of clinical signs and symptoms.

Table 1.4 Summary of performances of WHO clinical staging and the attempts for improvement.

Study	Parameter of WHO clinical staging performance measured		Suggestion for improvement of WHO staging criteria
Jaffar et al,2008	Sensitivity 52%	Specificity 68%	Urgent need for CD 4 + count
Morpeth S,2007	Sensitivity 85%	Specificity 63%	The presence of mucocutaneous manifestations
Lynen,2006	accuracy of the 2003 WHO criteria to start HAART		WHO stage III with weight loss
Teck et al, 2005	Proportion of WHO stage III/IV with CD4 + count ≤ 350 cells/μL		1-Advanced stage of HIV 2.Active or previous history of tuberculosis
Costello et al,2004	Sensitivity 33%		Anaemia,PPE and KS
Muhammad B,2003	Symptoms and signs predicting severe immunosuppression		PPE and KS
Malamba,1999	Symptoms and signs in WHO clinical axis and their corresponding CD4 + counts ≤ 200 cells/μL		A simple re-arrangement of a few clinical conditions

1.5 Justification

Previous studies have attempted to correlate clinical symptoms and signs with CD4 + counts (Malamba, 1999; Kassa, 1999; Morpeth, 2007). A recent study in Johannesburg screened 589 HIV positive women to determine eligibility for a clinical trial. The screening procedures included an assessment of clinical stage of HIV disease using WHO staging criteria (WHO, 2005) in potential participants; thus providing an opportunity to investigate the association between symptoms and signs and CD4 + count. To our knowledge, there are few studies that have provided data on people recruited from the community (i.e. not a hospital based data) (Jaffar, 2008, McGrath, 2007, Lynen, 2005).

1.6 Objectives

We undertook this secondary data analysis to:

1. Determine the distribution of symptoms and signs in women with HIV disease in Johannesburg, South Africa.

2. Determine the distribution of CD4 + count in women with HIV disease in Johannesburg, South Africa.

3. Identify the clinical symptoms and signs which best predict the need to initiate HAART (CD4 + count $\leq$ 200 cells/μL).

Chapter 2: Materials and Methods

2.1 Study Design

We conducted secondary data analysis using cross sectional screening data from 589 females participating in a randomized controlled clinical trial in HIV positive women (Delany, 2009).

2.2 Study Population

2.3.1 Inclusion criteria

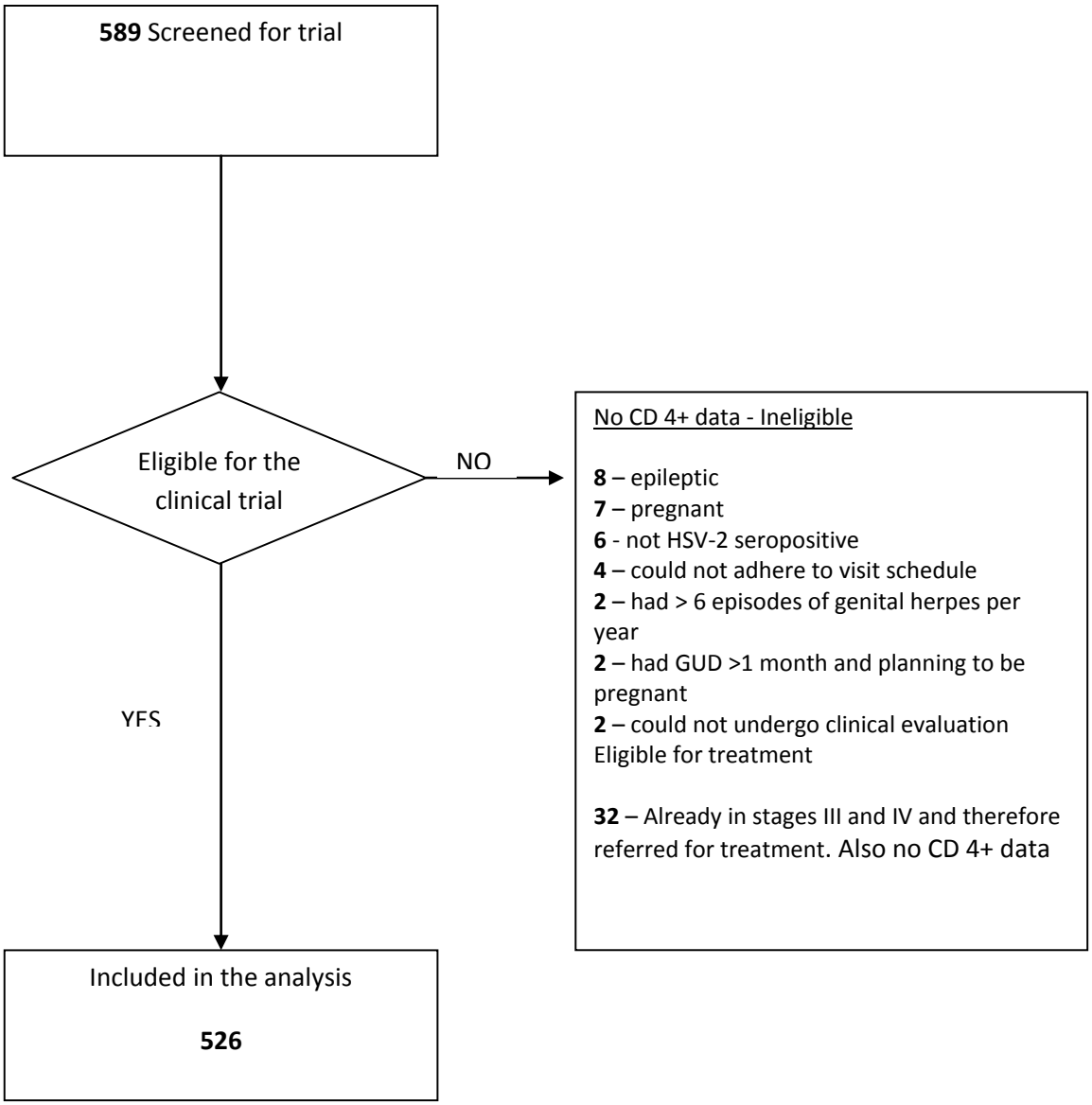
The trial included women who were: 18 years of age and above, HIV seropositive on two independent rapid tests, resident in Johannesburg for the period of the study, consenting to participate in the study and who had their CD4 + counts measured.

2.3.2 Exclusion criteria

The trial excluded women who were: pregnant, involved in another ongoing trial, epileptic,

not HSV-2 seropositive, could not adhere to visit schedule, had > 6 episodes of genital herpes per year, had genital urinary disease (GUD) >1 month and those who could not undergo a clinical evaluation.(Fig. 2.1)

Fig. 2.1 A flow chart showing how the sample was derived for analysis



2.3 Clinical Procedures

Potential participants were invited from local clinics and the surrounding community to attend the study clinic at RHRU at 17 Esselen Street Clinic in Johannesburg, for voluntary counselling and testing for HIV after giving written informed consent. Those who met the

eligibility criteria were then enrolled in the main clinical trial. At screening, participants were interviewed and examined by experienced doctors and nurses on specific HIV- related features. The doctors and nurses recorded the findings on a standardized checklist of possible HIV- related signs and symptoms which was based on the WHO criteria for clinical staging for HIV (Appendix 1) (WHO,1994). Some additional clinical features (e.g. fatigue or participant looking tired, dehydration etc) which are not strictly in the WHO clinical criteria were recorded by clinicians during physical examination. These features are incorporated in this analysis to examine their usefulness in predicting the outcome variable (i.e. CD4 + counts).

According to the trial protocol, blood was drawn for CD4 + count measurement in those who were in WHO clinical stages I/II. Those that were in WHO stages III/IV were referred for treatment immediately.

2.4 Laboratory Procedures

CD4 + counts were determined using the pan leucogating method (Wilja, 2002). All blood specimens were collected for processing, testing and/or storage at the Contract Laboratory Services (CLS) which is located within the University of the Witwatersrand Medical School at Parktown (approximately 5-10 minutes drive from the study clinic) in Johannesburg.

2.5 Statistical analysis

The data set was analysed using STATA 9. Descriptive statistics were used to summarize the distribution of symptoms and signs and CD 4 + counts among the study population.

2.5.1 Tests used to determine the predictive value of WHO clinical staging system.

Sensitivity, specificity, positive predictive values, negative predictive values, odds ratios and their 95% confidence intervals were used to determine the reliability of the WHO staging system in predicting the CD4 + count ≤ 200 cells/µL and < 350 cells/µL. Table 1.3 shows the categories of parameters and the subsequent formulae (Katzenellenbogen, Joubert and Abdool-Karim, 1997).

Table 2.1 Formulae to calculate the epidemiological diagnostic tests

	CD 4 <= 200	CD 4 > 200	Total
WHO stage III,IV	A	B	A+B
WHO stage I,II	C	D	C+D
Total	A+C	B+D	A+B+C+D

Sensitivity

Sensitivity was defined as the proportion of CD4 + counts ≤ 200 cells/µL classified as WHO stage III/IV.

Sensitivity = A /A+C x 100

Also the *cii* command in stata was used to give both the sensitivity (given as mean) and its 95% CI as: *cii (A+C) A*, where (A+C) = total binomial events, A = number of observed successes

Specificity

Specificity was defined as the proportion of CD4 + count > 200 classified as WHO stage I/ II

Specificity = D/B+D x 100

Also the cii command in stata was used to give specificity (given as mean) and the 95% CI across the mean

Positive Predictive value (PPV)

PPV was defined as the proportion of WHO stage I/II that have CD4 + count ≤ 200 cells/µL

PPV= A /A+B x 100

Also the cii command in stata was used to give the positive predictive value (given as mean) and the 95% CI across the mean

Negative Predictive Value (NPV)

The NPV was defined as the proportion of WHO stage III/IV that have CD4≥200 cells/µL

NPV= D /C+D x100

Also the cii command in Stata was used to give the positive predictive value (given as mean) and the 95% CI across the mean

2.5.2 Regression analyses

The assessment of the diagnostic value of the WHO criteria to predict CD4 + count (above or below 200 cells/µL) was evaluated using univariate logistic regression. The strength of association between symptoms and signs (clinical indicators) and CD 4 + count ≤ 200 cells/µL was determined by odds ratios and 95% confidence intervals. Adjusted analysis was performed to identify the symptoms and signs that were significantly associated with the CD count ≤ 200 cells/µL at a significance level of 0.2. These significant symptoms and signs at a univariate model were used to predict CD4 + ≤ 200 cells/µL by fitting multivariate models using logistic regression. The model adequacy was tested using **estat gof** command. The **link-test** was used to test for the presence of interaction among the symptoms and signs that persistently remained significantly predicting CD4+ count < 200 cells/µL at a multivariate

level. The above analysis was repeated to determine whether these indicators were still useful if the criteria for treatment were raised to CD4 + count ≤ 350 cells/μL. The remaining symptoms and signs not significantly predicting CD4 + count ≤ 200 or ≤350 cells/μL at univariate analysis were excluded from the analysis of sensitivity, specificity, positive and negative predictive values. If such statistical tests were performed on these symptoms and signs, they would neither have shown any significant results nor be able to correlate their presence with the CD 4 count ≤ 200 or ≤350 cells/μL.

2.6 Study sample size and power

Hypothesis:

We hypothesized that the use of WHO clinical staging system alone is feasible and appropriate to identify HIV positive asymptomatic women eligible for HAART (i.e. CD4 + count ≤ 200 cells/μL) in a South African setting.

The study sample size was determined by the method of "Estimated sample size for two-sample comparison of means" where a comparative study (Post, 1995) was considered. The Evaluation of WHO staging performance study had a mean CD4 + count of 455 cells/μL and a standard deviation and 252 while the study by Post (1995) had mean CD4 + count of 389 cells/μL and standard deviation and 161 respectively. The sample sizes of the former and the latter studies had a ratio of 3.5. Significance level of 0.05 was assumed; giving a required minimum sample size of 242 participants in order to have a power of 0.9708 to detect the differences between those with CD4 + count < or ≥ 200 cells/μL. Although this study is now a secondary (post-hoc) data analysis, the study power of 0.9708 is strong enough to test our hypothesis.

2.7 Ethical Considerations

Informed consent in the language of the patient was sought prior to study procedures. Patients were consulted in the key elements of the informed consent process viz. volunteer, option to withdraw without prejudice and risk benefits. Patients therefore filled and signed written informed consent at screening phase of the main trial. Confidentiality of individual study participants was observed by using unique identification numbers.

The investigator of this study obtained an approval from RHRU to use the data collected at the screening phase of the main trial. The protocol of this study was submitted to the University of the Witwatersrand Human Subjects Research Ethics Committee for clearance. The protocol was unconditionally approved by the HREC and given the ethical clearance reference number M080339.

Chapter 3: Results

3.1 Identification of the patient population included in the analysis

A total of 589 HIV infected women completed screening visits. Of 589 women assessed, 526 were assessed as clinically WHO stages I/II and 32 were in stages III/IV. Thirty one (31) were not assessed further because they did not meet other trial eligibility criteria (Fig.2.1).

3.2 Characteristics of Participants

Overall 73 (13%) of 526 participants had CD 4+ count < 200 cells/µL while 136 (26%) of 526 had CD 4 + count < 350 cells/µL. By stage 13% in stage I/II had CD 4+ <200 cells/µL compared to 3(50%) of 6 participants while 26% in stage I/II had CD 4+ < 350 cells/µL compared to 2 (33%) of 6 participants in stages III/IV. The mean age of all participants was 32, standard deviation 7 and the minimum and maximum age of 18 to 58 years respectively.

In this study population, the median time since diagnosis for all participants was 0.76 years (IQR: 0.09 - 3.00) i.e. 9 months. Among all patients (N=526) the most common symptoms were pain or difficulty in swallowing (dysphagia and possible oesophageal candidiasis) (18%) , cough for more than one month (8%) , and previous hospitalization in the past twelve months (10%). The most common causes for hospitalization in the preceding twelve months were obstetric and gynaecological problems (53%), pneumonia (14%), and tuberculosis (12%). Less frequently reported symptoms were diarrhoea (6%) and fever (4%). Overall, on examination the most common finding was swollen glands in the neck or armpits. The median CD4 + count overall was 403 cells/µL (IQR: 273-586). Table 3.1 summarises patient characteristics by WHO stage.

Table 3.1 indicates that the majority of study participants were in the early stages of HIV infection. Those in clinical stages I/II had been diagnosed more recently and had a higher median CD4 + count than those in clinical stages III/IV.

Table 3.1 Characteristics of participants and clinical profile

Characteristic	WHO Stage I/II N =520 N (%) or Median(IQR)	WHO Stage III/IV N=6 N (%) or Median(IQR)
Median time since HIV diagnosis (years)	0.8(0.1-3.0)	1.7 (0.1-1.8)
Symptom history		
Pain or difficulty with swallowing	96(18)	1(17)
Hospitalized in the previous 12 months	51(10)	0(00)
Cough > 1 month	42(8)	1(17)
Night sweats > 1 month	25(5)	1(17)
Headache > 1 month	24(5)	1(17)
Confined to bed > 50% the day time	25(5)	1(17)
(Substantial unintentional weight loss ≥ 10% body weight	17(3)	2(33)
Diarrhoea > 1 month (i.e. ≥ 3 loose stools/day)	8(2)	1(17)
Persistent genital or oral sores >1 month	7(2)	2(33)
History of Tuberculosis	27(5)	1(17)
Generalized body rash	34(7)	3(50)
Examination findings		
Swollen glands in the neck/axillae	65(13)	2(33)
Lymphadenopathy	40(8)	0(00)
Oral thrush (candida)	21(4)	2(33)
Zoster (shingles)	22(4)	1(17)
Participant looks tired	10(2)	0(00)
Generalized skin rash	12(2)	1(17)
Median CD 4+ count [cells/μL (IQR)]	405(279 -588)	211 (174 -248)
CD4+ count (cells/μL)		
< 200	70(13)	3(50)
200-350	134(26)	2(33)
>350	316 (61)	1(17)

3.3 Patients with CD4 + count < 200 cells/µL while in WHO clinical stages I and II

Seventy three (14 %) of the study population had CD 4+ count < 200 cells/µL.

Table 3.1 indicates that 70 (13%) of 520 women were in WHO clinical stages I and II and they had CD4 + count < 200 cells/µL. One hundred thirty four (26%) of 520 women who had CD4 + counts in the category < 350 cells/µL would become eligible for ARV if treatment guidelines were to change.

3.4 Diagnostic value of WHO clinical criteria

We assessed the diagnostic value of WHO staging in this population. The results are presented in table 3.2. Table 3.2 shows a low sensitivity of WHO clinical staging in predicting CD4 +count < 200 cells/µL and < 350 cells/µL but a high specificity. It also shows a higher specificity and a positive predictive value from a CD 4 + counts 200 to 350 cells/µL. However, confidence intervals are wide because of small numbers of the patients with CD4 + counts < 200 and also ≤ 350 cells/µL.

Table 3.2 The sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of WHO clinical stage against CD4 + counts for the assessment of eligibility for HAART.

	CD4 count × 10^6/l (number of subjects)		Total	Sens	Spec	PPV	NPV
WHO stage	**<200**	**≥200**		**[Percent (95% CI)]**			
III,IV	3	3	6				
I,II	70	450	520	4(1-12)	99(98-100)	50(12-88)	87(83-89)
Total	73	453					
	<350	**≥350**					
III,IV	5	1	6	2(1-6)	99(98-100)	83(36-99)	61(57-65)
I,II	203	317	520				
Total	208	318					

Table 3.2 indicates that the likelihood of identifying an HIV patient with WHO clinical stage I/II and having CD4 + counts ≤ 200 cells/μL is 4% while identifying a patient having CD4 + count ≤ 350 cells/μL is 2%.

Table 3.3 The symptoms and signs predictive of the need to start HAART treatment (CD4 + count ≤ 200 cells/µL)

Clinical Indicator	CD4 <200 (%) N=73	CD4 ≥200 (%) N=453	Measure of Association OR (95% CI)	p-value	Adjusted Measure of Association OR(95%CI)	p value
<u>On History:</u> Pain or difficulty with swallowing	9 (13)	88(20)	0.6 (0.3-1.2)	0.173	0.4(0.2-1.2)	0.095
Fever > 1 month	3 (4)	10(2)	1.9 (0.5-7.2)	0.329	0.3(0.1-4.6)	0.415
Cough > 1 month	11 (15)	32(7)	2.5 (1.2-5.3)	0.014	2.6(1.2-5.6)	0.017
History of TB	7 (10)	21(5)	2.2 (0.9-5.4)	0.081	1.7(0.5-5.7)	0.355
Night sweats > 1 month	5 (7)	21(5)	1.5 (0.6- 4.2)	0.405	0.8(0.2-4.4)	0.866
History of Generalized body rash	10(14)	27(6)	2.5 (1.2- 5.5)	0.018	2.9(1.3-6.7)	0.011
Persistent genital or oral sores >1 month	3 (4)	6(1)	3.2 (0.8-13.3)	0.102	0.6(0.1-13.6)	0.725
Diarrhoea > 1 month	3 (4)	6(1)	3.2 (0.8-13.3)	0.102	4.9(1.4-50.7)	0.179
<u>On Examination</u>:						
Oral thrush (candida)	7(10)	16(4)	2.9 (1.2-7.4)	0.022	2.6(1.1-6.9)	0.047
Swollen glands in the neck or axillae	11(15)	56 (12)	1.3 (0.6-2.6)	0.492	0.9(0.4-2.5)	0.955
Substantial unintentional wt loss	10 (5)	15(3)	1.7 (0.6-5.4)	0.228	1.3(0.1-45.6)	0.873
Fatigue (general body malaise)	4 (6)	6(1)	4.4 (1.2-15.9)	0.025	4.9(1.4-18.1)	0.015
Pallor	2 (3)	4 (1)	3.2 (0.6-17.8)	0.184	1.1(0.1-26.9)	0.931
Dehydration	2 (3)	1(1)	12.9 (1.2-144.3)	0.038	14.6(1.3-163.8)	0.030
Generalized skin rash	5 (7)	8 (2)	4.2 (1.3-13.3)	0.014	3.6 (1.1-11.8)	0.034

3.5 Symptoms and/or signs associated with CD4 + count < 200 and < 350 cells/µL.

We conducted an analysis to determine the symptoms and signs that predict the need for HAART initiation in this study population (Table 3.3). In a univariate logistic regression analysis, cough > 1 month, history of tuberculosis, history of generalized body rash, persistent genital or oral sores > 1 month, diarrhoea > 1 month, oral thrush, herpes zoster, general body malaise, dehydration and generalized skin rash were associated with CD4 + count < 200 cells/µL. The significant symptoms/signs persistently predicting CD4 + count < 200 cells/µL at a multivariate model were dehydration (OR= 14.6), skin rash (OR= 3.6), candida (OR = 2.6), cough>1 month (OR= 2.6) and history of generalized body rash (OR= 2.9). The model was adequate and there were no interaction terms detected.

Table 3.4. The distribution of CD 4 + counts at a cut – off ≤ 350 cells/μL **and clinical indicators that remained significant in predicting CD4 count < 350** cells/μL**.**

Clinical Indicator	CD4 <350 (%) N=73	CD4 ≥350 (%) N=453	Measure of Association OR (95% CI)	p-value	Adjusted Measure of Association OR(95%CI)	p value
On History: Pain or difficulty with swallowing	34 (16)	63 (20)	0.8 (0.5-1.3)	0.329	0.7(0.4-1.2)	0.157
Fever > 1 month	7 (3)	6 (28)	1.8 (0.6-5.5)	0.288	0.6(0.1-3.2)	0.542
Cough >1 month	23 (11)	20 (6)	1.9 (1-3.5)	0.050	1.8(0.8-4.4)	0.172
History of TB	17 (8)	11(3)	2.5 (1.1-5.4)	0.021	2.4(1.1-5.2)	0.034
Night sweats > 1 month	10 (5)	16 (5)	1 (0.4- 2.1)	0.918	0.6(0.2-2.1)	0.464
History of generalized body rash	18 (9)	19 (6)	1.5 (0.8- 2.9)	0.236	1.2(0.4-3.1)	0.758
Persistent genital oral sores >1 month	4(2)	5(2)	1.2 (0.3-4.6)	0.757	0.2(0.1-3.7)	0.293
Diarrhoea > 1 month	5(2)	4(1)	1.9 (0.5-7.3)	0.326	1.3(0.2-10.8)	0.782
On Examination:						
Oral thrush (candida)	16 (8)	7 (2)	3.7 (1.5-9.2)	0.004	3.2 (1.2-7.9)	0.015
Swollen glands in the neck or axillae	30 (14)	37 (12)	1.3 (0.8-2.2)	0.338	1.1(0.6-2.2)	0.706
Substantial unintentional wt loss	10 (5)	9 (3)	1.8 (0.7-4.4)	0.228	1.8(0.4-7.4)	0.401
Fatigue (general body malaise)	6(3)	4(1)	2.3(0.7-8.4)	0.191	1.2(0.2-9.5)	0.833
Pallor	4(2)	2(1)	3.1(0.6-17.1)	0.193	2.3(0.1-36.9)	0.558
Herpes Zoster	6 (8)	17 (4)	2.3 (0.9-6.1)	0.086	0.2(0.1-2.3)	0.200
Generalized skin rash	10 (5)	3 (1)	5.4 (1.5-19.7)	0.012	4.5 (1.2-17.0)	0.026

We again conducted an analysis to determine the symptoms and signs which where still useful in predicting the need for treatment at higher CD4 + counts such as CD4 + count ≤ 350 cells/μL, a threshold level recently recommended by WHO for starting HAART (Table 3.4). At a significance level of 0.2 in a univariate analysis, cough for more than one month, history of tuberculosis, generalized body rash, oral thrush, general body malaise, pallor, herpes zoster and generalized skin rash were the symptoms and signs predicting CD4 + count < 350 cells/μL. The significant symptoms/signs persistently predicting CD4 + count < 350 cells/μL at a multivariate model were, candida (OR= 3.2) and generalized skin rash (OR = 4.5) and history of tuberculosis (OR= 2.4). The final model was found to be adequate with no interacting symptoms and signs in predicting CD4 + count 350 cells/μL.

3.6 Sensitivity and specificity of modified clinical staging

We conducted an analysis of sensitivity and specificity on clinical features that predicted CD4 + count < 200 and < 350 cells/µL on adjusted analyses.

Table 3.5 Sensitivity, Specificity, PPV and NPV for the indicators for multivariate significant variables at CD4 + count cut-off 200 cells/µL and 350 cells/µL.

Clinical Indicators	CD 4 Count (no. of subjects)		Sensitivity [Percent(95 % CI)]	Specificity [Percent(95 % CI)]	PPV [Percent(95% CI)]	NPV [Percent(95% CI)]
	<200 (N=73)	>200(N=453)				
Generalized skin rash	5 (7%)	8 (2%)	7(2-15)	98(97-99)	38(14-68)	88(84-90)
Oral thrush	7(10%)	16(4%)	10(3-19)	96(94-98)	30(13-53)	87(84-90)
Dehydration	2(3%)	1(1%)	3(1-9)	99(98-99.9)	67(10-90)	86(83-89)
	<350 (N=208)	>350(N=318)				
Generalized skin rash	10 (5%)	3 (1%)	5(2-9)	99(97-99.8)	76(46-95)	62(57-66)
Oral thrush	4 (2%)	6 (2%)	2(1-5)	98(96-99)	40(12-74)	60(56-65)
History of TB	17(8%)	11(3%)	8(5-13)	97(94-98)	61(41-78)	62(57-66)

Table 3.5 shows low sensitivity and low positive predictive values of the symptoms and signs that predict CD4 + count < 200 cells/µL. The specificity and negative predictive values were fairly high. These clinical features were significant on adjusted analysis. Oral thrush (candida) has the highest sensitivity (10%) of the three clinical features. Table 3.5 further shows generally a low sensitivity of the clinical features in predicting CD4 + count < 350 cells/µL. The positive predictive values increased at the CD4 + count threshold of 350

cells/μL while the NPV decreased in comparison to those of the CD4 + count threshold of 200 cells/μL. Sensitivity decreased for generalized skin rash while specificity increased.

Chapter 4: Discussion

We set out to investigate which signs and symptoms were commonly associated with HIV infection that could be used to best predict immunosuppression among asymptomatic HIV infected women in South Africa, and therefore the need for HAART. We hypothesized that the use of WHO clinical staging alone is feasible and appropriate to determine those eligible for HAART in a South African setting. Our hypothesis was not confirmed. Overall there was a very low sensitivity and specificity of the WHO clinical staging in identifying those in need of HAART initiation.

4.1 Percentage of HAART eligible patients not detected by WHO criteria

This analysis adds more information on the currently available limited data on how well the WHO HIV clinical staging criteria performs in correctly identifying patients needing HAART. Our data have shown that WHO clinical staging is a poor substitute for CD4 + count determination.

In this study of HIV positive women recruited from the community, 98.8% were in WHO clinical stages I and II and had a median CD4 + count of 405 cells/µL (IQR: 279, 588).These results reveal that even in this relatively healthy group 14% had CD4 + count < 200 cells/µL and required treatment. They would have been deferred HAART treatment on the basis of WHO staging alone. A recent study (Kagaayi et al, 2007) conducted in Rakai, Uganda, showed that 49% of patients with CD4 + count < 200 cells/µL were classified as WHO stage I/ II. Other studies from Uganda and Ethiopia have had similar findings where between 27-49 % of patients assessed as WHO stage I/II had CD4 + count < 200 cells/µL and would not have been started on treatment on clinical assessment alone (Kassa, 1999; Jaffar, 2008).This

could be because of low symptom recognition, other concurrent illnesses, lack of access to diagnosis and poor training of health care providers.

4.2 Performance of WHO criteria to predict initiation of HAART

This study showed that WHO clinical staging had sensitivity, specificity, PPV and NPV of 4%,99%,50% and 87% respectively in predicting CD4 + T-cell count <200 cells/µL. Several studies (French,1996; Costello,2005; Martinson,2005; Kagaayi,2007 and Jaffar,2008) also found a low sensitivity of 76%; 31.8%; 24%; 51%; and 52%, respectively in various settings, all indicating weakness of WHO clinical staging to accurately predict initiation of HAART in poorly-resourced countries.

In the study by French (1999) he found 76% sensitivity and 65% specificity for predicting a CD4+ T-cell count <200 cells/µL, positive predictive value of 56%, negative predictive value 78%.These results are similar to the current study in terms of PPV and NPV. The low sensitivity in our current analysis can best be explained by the fact that most of our patients were asymptomatic and were predominantly in the early WHO clinical stages; and the fact that CD 4 + counts were taken from those who were in WHO clinical stages I/II as per protocol of the main clinical trial.

Another study done in Uganda (Jaffar et al, 2008) found that the sensitivity, specificity, positive and negative predictive values predicting CD 4 + T-cell count <200 cells/µL was found to be 52% (95% CI 50, 54%), 68% (95% CI 66, 70%), 64 % and 56% respectively. A bigger sample size for the study by Jaffar (N= 4302) could explain a narrower confidence

intervals as opposed to our rather smaller sample size (N=526) which led to our wider confidence intervals and hence less precision.

A study done in Thailand (Costello et al, 2005) among women found that the December 2003 WHO guidelines had a sensitivity of 31.8% to detect persons with a CD4 + count < 200 cells/µL in this HIV-infected population. This is clearly a low sensitivity as well. However the use of a TLC <1500 cells/µl or TLC < 2000 cells/µL combined with anaemia or WHO stage II infection doubled the sensitivity to detect persons with a CD4 count < 200 cells/µL (63.0% in men, 68.2% in women) with less than a 6 % decrease in specificity. The Costello study combined the various threshold points of TLC (TLC < 1500 cells/µL or TLC <2000 cells/µL or < 1800 cells/µL) combined with anaemia and BMI to determine the sensitivity and specificity of WHO staging in predicting CD4 + count < 200 cells/µL and < 350 cells/µL. This combination doubled the sensitivity of WHO criteria to predict CD 4 < 200 cells/µL and < 350 cells/µL.Our data, in contrast, utilized the WHO classification criteria (symptoms and signs) only to determine CD4 + count < 200 cells/µL and < 350 cells/µL and had a low sensitivity though high specificity, indicating the limitation of WHO staging for screening people who are clinically well as compared to those who are debilitated for treatment eligibility.

Our data have shown that the WHO staging is useful for identifying those with obvious symptoms and signs (i.e. clinically ill) who need treatment but not so useful for clinically well people who would also benefit from treatment. It thus follows from our data that clinical assessment alone among the HIV positive from the general population has proved to be weak in identifying eligible persons for HAART. This is in agreement with earlier reports that suggested a combination of routine, affordable parameters like TLC, haemoglobin and BMI

to the clinical parameters to further improve the sensitivity and specificity of WHO clinical staging system. (Costello et al, 2005).

Kagaayi et al (2007) in Uganda also showed that the sensitivity to predict CD4 + count of 200 cells/µL or less was 51% and specificity was 88 %. The positive predictive value was 64 % and the negative predictive value was 81%.Clinical criteria missed half the patients with CD4 + cell counts of 200 cells/µL or less, highlighting the importance of CD4 + cell measurements for the scale-up of ART provision in resource-limited settings. This is another evidence for the weakness of such a tool in identifying those eligible for treatment. Of careful note here is that Kagaayi analysed data on patients seen in the Rakai Health Sciences Programme (RHSP) community-based ART programme to assess whether WHO clinical stages III/IV could be used to identify individuals with CD4 + cell counts of 200 cells/µL or less. This implies that these clinical stages were already advanced (i.e. stages III/IV) as opposed to our data which had patients in clinical stages I/II.

Martinson N et al (2005) conducted a study in primary healthcare facilities in South Africa which showed that 24% of patients classified as WHO stage I and 46% classified as stage II had CD4 + cell counts of 200 cells/µL or less. A substantial proportion of stages I and II cases would not have been initiated on ART if therapy was based on clinical criteria alone. This finding is a further evidence of the inability of WHO clinical criteria alone in identifying asymptomatic infected persons from the general community who are eligible for HAART.

4.3 Symptoms and signs significantly predicting HAART initiation (i.e. CD 4 < 200 cells/µL) according to the current South African guidelines

In this study the identified clinical indicators for CD4 + count < 200 cells/µL after adjusting for all factors were generalized skin rash, dehydration and oral thrush (candida). We note that patients likely to seek care for these conditions may not know their HIV status; and these conditions are strong predictors of need for treatment. Amirali et al (2004) also identified exactly the same symptoms and signs among hospitalized HIV positive patients in Hindu-Mandal Hospital in Dar es Salaam, Tanzania, consistent with our findings in these women from the general community in Johannesburg. South Africa.

The finding of a non - specific generalized skin rash on examination was associated with low CD4 + count (OR= 4.2, 95% CI:1-13).This is consistent with a study by Bakari et al (2003) among 716 police officers in Dar es Salaam,Tanzania.Bakari found that among 191 police officers, 26.7% had at least one skin diagnosis. HIV-infected police officers had significantly higher prevalence of skin diseases than HIV-uninfected police officers (42% vs 26 %, p = 0.002).The authors also found that PPE, herpes zoster and KS strongly suggested underlying HIV-related immunodeficiency.

Mbuagbaw et al (2004) studied the patterns of skin manifestations and their relationships with CD4 + counts among 384 HIV/AIDS patients in Cameroon. The authors found that up to 264 (68.8%) patients presented with at least one type of skin problem. Generalized prurigo, oral candidiasis, herpes zoster, and vaginal candidiasis were the most common skin problems associated with mean CD4 + count (128 ± 85 cells/µL) and mean viral load (79,433 copies/mL) (P < 0.001).Generalized skin rash was associated with lower mean CD4 + cell counts (78 ± 66 cells/µL, P < 0.001).

A study by Machekano et al (2002) among 447 HIV – infected men in Zimbabwe to determine the clinical signs and symptoms in the assessment of immunodeficiency in men with HIV infection in Harare showed that skin infections and enlarged lymph nodes had the strongest prognostic effect in all the models considered. In the current study generalized skin rash remained significant at both CD4 + count threshold of 200 and 350 cells/µL confirming its importance in immunosupressed persons. In the same study Machekano (2002) indicates that skin infections were more than twice as likely to be reported in patients with CD4 + counts < 200 cells/µL compared to patients with CD4 + cell counts >200 cells/µL.Skin manifestation as a generalized rash is a strong marker of severe immunosuppression in the multivariate models in the current study at both thresholds of CD 4 + counts 200 and 350 cells/µL.

The possible explanation for skin manifestation being common at low CD4 + count is due to altered normal flora along side immunodeficiency. Other mechanisms could be auto immune phenomena like vitiligo, alopecia, etc which are predominantly due to immune dysregulation seen in HIV at low CD4 + count (Cho M, 1995). The other explanation could be a systemic immune dysfunction, as seen in HIV infection, where the influx of CD4 + lymphocytes to the perifollicular regions of skin when the CD4/CD8 ratio is low leads to skin inflammation (Stewart, 1993).

Dehydration was an additional clinical feature not strictly in WHO criteria but was found to be significant in predicting CD4 + count < 200 cells/µL in this study population. Although it featured in our adjusted analyses it was based on a small number of patients (4 out of over 500). The possible explanation for dehydration in HIV infection is due anorexia, dysphagia and chronic diarrhea.

Oral thrush was found to predict both CD4 + counts < 200 and < 350 cells/µL.It is a marker of HIV infection that is bound to occur especially during advanced stage of immunosupression (Carré et al, 1998). Oropharyngeal candidiasis is the most common fungal and opportunistic infection in human immunodeficiency virus - infected individuals, affecting nearly 90% of subjects at some stage during the course of HIV disease progression (De Repentigny et al, 2004).

In this study oral thrush was identified to predict CD4 + counts at both thresholds of < 200 and < 350 cells/µL.This is concordant with other reports (Carré et al 1998; Munoz-Perez, 2002 and Sud et al, 2009). In the study by Carré among homosexual men, the occurrence of oral thrush at a CD 4 + count > 200 cells/µL signifies that oral thrush remained an important risk factor, underlining the predictive value of clinical signs at CD4 + count higher than 200 cells/µL. In another study by Erkose (2007) it was reported that 53/64 i.e. (83%) HIV infected patients were colonized by oral candida in Istanbul, Turkey. This study shows no correlation between CD 4 + count and oral candidiasis although they report a high prevalence of oral candida colonization (83%) in their study population. However he noted, from his study of 64 HIV individuals, that the failure to show an association may be explained by his small sample size and hence less statistical power.

In one study in Zimbabwe, oral candidiasis was the most common lesion diagnosed in nearly one quarter of 320 HIV-infected women. It was also shown that of those with oral candidiasis, one-third of them had a CD4 + count < 200 cells/µL. (Chidzonga et al, 2008). Mbuagbaw et al (2004) also found that in Cameroon oral candidiasis was associated with CD 4 count < 200 cells/µL ($p<0.02$).

So far these studies show contrasting findings with regard to relationship between CD 4+ counts and oral thrush. The most important message here, however, is that as oral thrush

occurs in both patients with CD4 + > 200 and as well as in CD 4+ < 200 it lacks specifity as a sign of AIDS. Thrush (candidiasis) is seen at these levels of CD 4 + counts because patients often develop dysregulated cytokine production, a dysfunction in the local oral immunity, superimposed on a weakened cell-mediated immunity and depletion of CD4 + T cells (Egusa,2008). The role of defective dendritic cells and CD4 + T cells in impaired induction of protective immunity has been documented as the pathogenesis of thrush (de Repentigny, 2009).

4.4 Symptoms and signs significantly predicting HAART initiation (i.e. CD 4 < 350 cells/µL) according to the new WHO recommendation

Generalized skin rash, history of tuberculosis and oral thrush were the symptoms and signs that predicted CD4 + counts < 350 cells/µL after a multivariate analysis. It is observed that generalized skin rash remained significant at both CD4 + count thresholds of 200 and 350 cells/µL. This finding signifies that dermatological manifestations are an early and important clue of significant immunosupression (Bakari et al 2003).

History of TB was an important predictor if treatment is to be initated at higher CD4 + count levels. HIV infection and related opportunistic infections, particularly tuberculosis and upper respiratory tract infections, have become the leading cause of death in much of sub-Saharan Africa (Machekano R, 2002).Machekano also noted that currently, most health care providers have limited access to laboratory diagnosis and monitoring of HIV infection. They rely heavily on clinical manifestations of the disease.

Literature shows a challenge of making a diagnosis of tuberculosis at the CD4 + cell count threshold of < 200 cells/µL (Mtei, 2005).This analysis has indicated a history of tuberculosis to predict CD4 + count < 350 cells/µL. This is a further evidence of the relative easiness of making a diagnosis of TB at a CD4 + count >200 cells/µL. A study conducted in Malawi (Zachariah R et al, 2005) showed that pulmonary TB was present in 98% (51/52) among HIV positive individuals presenting with and without WHO defining diseases, among those having CD4 + count < 350 cells/µL. Tuberculosis was also noted by another researcher in Tanzania (Mtei, 2005) to be present while CD4 + count was still above 200 cells/µL, a finding that is concordant with this study. Narain (2004) showed that HIV is considered to be the most important risk factor to progression to active TB among those infected both with TB and HIV. As a result, TB is the most common life threatening opportunistic infection associated with HIV, and the biggest cause of death among patients with HIV. The deadly relationship between HIV and TB results from each potentiating the effect of the other. In the context of this analysis, the relationship between TB and HIV is an important finding.

4.5 Practical Implications for Screening for a History of TB.

Our data has shown that cough > 1 month was significant in predicting CD4 + count < 200 cells/µL while a history of TB predicted CD4 + count < 350 cells/µL.HIV infection is therefore a risk factor for TB disease (Tribble,2009). The implications for screening for a history of TB are for diagnosis and treatment among TB/HIV co-infected. The following are measures (MMWR/CDC, 1998) are implied:

1. Early diagnosis and effective treatment of TB among HIV-infected patients are critical for curing TB, minimizing the negative effects of TB on the course of HIV, and interrupting the transmission of Mycobacterium tuberculosis to other persons in the community.

2. All HIV-infected persons at risk for infection with M. tuberculosis must be carefully evaluated and, if indicated, administered therapy to prevent the progression of latent infection to active TB disease and avoid the complications associated with HIV-related TB.

3. All HIV-infected patients undergoing treatment for TB should be evaluated for antiretroviral therapy, because most patients with HIV-related TB are candidates for concurrent administration of antituberculosis and antiretroviral drug therapies. However, the use of rifampin with protease inhibitors or non-nucleoside reverse transcriptase inhibitors is contraindicated.

4. Missed opportunities for HIV treatment at the time of TB treatment is a common phenomenon underscoring the need for integration of TB and HIV diagnostic services (Tribble, 2009).

Chapter 5: Strengths and Limitations

5.1 The strengths of this study

These include:

1. The data are not hospital based.
2. A study population was recruited from the general population and so it was a generally healthy population, thus giving a picture of what is the situation of the need among the HIV infected in the general population.

5.2 Limitations of the study

1. The study population comprised of women solely who are HIV-1 seropositive and HSV-2 co-infected; thus may not be generalizable to other HIV only infected women in the general population, men or children.
2. Rarity of some important symptoms and signs as the study population was still asymptomatic.
3. Measurement (information) bias. The low index of suspicion of some clinical features e.g. oral hairy leukoplakia (Schiødt, 1990) which are normally not frequently detected by clinicians during physical examination. This could lead to underestimate the number of symptoms/signs that predict CD4 + count < 200 cells/μL.
4. Very few patients were in WHO clinical stages III/IV. The small numbers in this category could make some associations to be due to chance and lead to a lack of accuracy in sensitivity calculations.

5. Biases of the recruitment and the exclusion: Patients in WHO stages I/II only had their CD 4 + count measured at the screening phase of the clinical trial. Patients with WHO clinical stages III/IV were immediately referred for treatment. This led to a majority of the study population analysed being in WHO stages I/II.

Chapter 6: Conclusions and Recommendations

In summary, these results show that the WHO clinical staging is inadequate as a tool to predict the need for initiating ART in a population of women who are still asymptomatic. If clinical staging is used alone as many as 13% of women would have gone untreated. Initiation of HAART would have been deferred in these patients until they reached a more advanced HIV clinical stage when treatment outcomes are likely to be less successful (Wilkin, 2008). This study shows that certain signs are strongly associated with the need to initiate treatment. These conditions are relatively infrequent in the general population, but when observed should alert clinicians to the need for treatment in these patients. Of interest was the finding that a history of TB is strongly associated with a CD4 < 350 cells/μL and that this may be a useful indicator for initiating HIV treatment in a South African population.

Given the fact that the HIV incidence is still rising it can be expected that the health care facilities will be over burdened in the near future by HIV and the associated opportunistic infections in the near future. (Dorrington, 2004, Kober K and Van Damme W, 2004). From this study, we therefore suggest encouraging more HIV positive people to come forward for treatment through intensifying campaigns for VCT for early diagnosis and treatment. Those eligible will be identified and brought to treatment as early as possible.

Given the findings of this study it is recommended that CD4 + count testing should be the most reliable indicator of when to start treatment. Where testing is restricted:

1. CD 4 + count measurements could be targeted at those without obvious predictors of immunocompromise.

2. The overall diagnostic accuracy (i.e. the ability to detect correctly all those who require and do not require HAART) of WHO staging criteria could increase using the

combination of other parameters like BMI, haemoglobin, TLC and an active WHO indicator disease (Zachariah R, 2005; Erhabor, 2006). Simple, inexpensive laboratory determination of haemoglobin, and a non laboratory procedure like BMI determination should be combined with the symptom/signs identified to initiate HAART. The thresholds of such parameters with these identified symptoms and signs predicting CD4 + counts < 350 cells/µL are a subject of the next investigation although not looked at in this study.

We thus conclude by having shown symptoms and signs which best predict the need for HAART initiation in the absence of CD4 + measurement to be generalized skin rash, dehydration and oral thrush (candida).We recommend that clinical assessment alone should not replace CD4 + testing in identifying asymptomatic people in the general population that need treatment by HAART. This calls for more campaign for VCT and more resource allocation in HIV care and treatment.

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8.0 Appendices

Appendix E.1 QUESTIONNAIRE USED FOR THE MAIN TRIAL: THE EFFECT OF ANTI-HERPETIC SUPPRESSIVE THERAPY ON HIV SHEDDING IN SOUTH AFRICAN WOMEN WHO ARE SEROPOSITIVE FOR HIV AND HSV2: A RANDOMISED CONTROLLED TRIAL

[visitCode] Visit code ##

We want to learn about aspects of your health related to your HIV infection.

1.	**[firsthiv]** Date of first known positive test for HIV? (dd/mmm/yy) **[inhivdate]** – Incomplete date e.g (01-JAN-YYYY)	☐☐/☐☐☐/☐☐

2. **In the past 12 months, have you had any of the following health problems?**

If "Yes" to shaded items, then participant is ineligible (WHO Stage 3-4).

		Yes	**No**	**Don't know**
2a	**[sore]** Persistent genital OR oral sores > 1 month?	1	2	98
2b	**[wtloss]** Substantial <u>unintentional</u> weight loss (>= 10% body weight)?	1	2	98
2c	**[diamth]** Diarrhea > 1 month (>= 3 loose stools/day)?	1	2	98

2d	**[diawk]** Diarrhea > 1 week but < 1 month?	1	2	98
2e	**[pain]** Pain or difficulty with swallowing?	1	2	98
2f	**[fevmth]** Fever > 1 month?	1	2	98
2g	**[fevwk]** Fever > 1 week but < 1 month?	1	2	98
2h	**[coughmth]** Cough > 1 month?	1	2	98
2i	**[coughwk]** Cough > 1 week but < 1 month?	1	2	98
2j	**[sweatmth]** Night sweats > 1 month	1	2	98
2k	**[sweatwk]** Night sweats > 1 week but < 1 month	1	2	98
2l	**[Headmth]** Headache > 1 month?	1	2	98
2m	**[Headwk]** Headache > 1 week but < 1 month?	1	2	98
2n	**[Bed]** Confined to bed for more than half the daytime	1	2	98
2o	**[Rash]** Generalized body rash?	1	2	98
2p	**[Glands]** Swollen glands in the neck or armpits?	1	2	98

3. In the past 12 months, have you been diagnosed by a health care provider with…?

If "Yes" to shaded items, then participant is ineligible

		Yes	No	Don't know
3a	**[seizure]** Seizures	1	2	98
3b	**[renal]** Renal failure	1	2	98
3c	**[pneumo]** Pneumonia	1	2	98
3d	**[meningitis]** Meningitis	1	2	98
3e	**[tb]** Tuberculosis (TB)	1	2	98
3f	**[candida]** Oral thrush (Candida)	1	2	98
3g	**[shingles]** Zoster (shingles)	1	2	98
3h	**[kaposis]** Kaposi's sarcoma	1	2	98

3i	**[otheropp]** Other opportunistic infections **[speopp]** Specify:	1	2	98

4	**[hosp]** In the past 12 months, have you been hospitalized for any condition?	**Yes=1** **No=2** **Don't know=98**	Go to SPE
4a	**[nohosp]** If YES, how many times have you been hospitalized in the past 12 months?	☐☐☐	
4b	What was the reason for admission?	**[admit1]** 1.__ **TEXT** _____ **[admit2]** 2.__ **TEXT** _____ **[admit3]** 3.__**TEXT** _____	

[ptid] Participant ID ☐☐☐☐☐ - ☐**(S-####-#)** Visit date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)

	[ptwt] Patient weight	☐☐☐.☐ kg

2.	**General examination**	**Yes**	**No**	**Not examined**
a	**[tired]** Participant looks tired	1	2	88
b	**[temp]** Elevated temperature	1	2	88
c	**[pallor]** Pallor	1	2	88
d	**[jaundice]** Jaundice	1	2	88
e	**[dehyd]** Dehydration	1	2	88
f	**[lymph]** Lymphadenopathy (in ≥ 2 extragenital sites)	1	2	88
g	**[edema]** Oedema	1	2	88

3.	**Skin**	**Yes**	**No**	**Not examined**
a	**[skinrash]** Generalised skin rash	1	2	88
b	**[skinzos]** Zoster	1	2	88
c	**[skinkap]** Kaposi's sarcoma → If YES, ineligible	1	2	88
d	**[othskin]** Other, **[speskin]** specify: **TEXT**	1	2	88

[ptid] Participant ID ☐☐☐☐☐ - ☐**(S-####-#)** Visit date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)

4.	**Oral exam**	**Yes**	**No**	**Not examined**
a	**[oralthrush]** Thrush → If YES, ineligible	1	2	88
b	**[ohl]** OHL (oral hairy leukoplakia) → If YES, ineligible	1	2	88
c	**[oralkap]** Kaposi's sarcoma → If YES, ineligible	1	2	88
d	**[oralulcer]** Ulcers	1	2	88
e	**[ginperid]** Gingivitis/periodontitis	1	2	88
f	**[othoral]** Other **[speoral]** specify: **TEXT**	1	2	88

5.	**Chest**	**Yes**	**No**	**Not examined**
a	**[tachyp]** Tachypnoea	1	2	88
b	**[cynosis]** Cyanosis	1	2	88
c	**[pleural]** Pleural effusion	1	2	88
d	**[bronchial]** Signs of bronchial or parenchymal disease	1	2	88
e	**[othchest]** Other **[spechest]** specify: **TEXT**	1	2	88

[ptid] Participant ID ☐☐☐☐☐ - ☐**(S-####-#)** Visit date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)

6.	**Abdomen**	**Yes**	**No**	**Not examined**
a	**[hepato]** Hepatomegaly	1	2	88
b	**[spleno]** Splenomegaly	1	2	88
c	**[ascites]** Ascites	1	2	88
d	**[abdm]** Abdominal mass	1	2	88

7.	**Nervous system**	**Yes**	**No**	**Not examined**
a	**[meng]** Meningism	1	2	88
b	**[abngait]** Abnormal gait	1	2	88
c	**[periph]** Peripheral neuropathy	1	2	88
d	**[Palsy]** Visible palsy/paresis	1	2	88
e	**[visd]** Visual disturbances	1	2	88
f	**[cogd]** Cognitive deficit	1	2	88

Comments:

[ptid] Participant ID ☐☐☐☐☐ - ☐**(S-####-#)** Visit date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)

FINAL ASSESSMENT OF HIV DISEASE STATUS			
8	**[wstage]** Indicate stage of HIV disease based on WHO Clinical Staging System	**Stage 1/2 = 1**	→ Collect CD4+
		Stage 3/4 = 2	→ **Ineligible**

[ptid] Participant ID ☐☐☐☐☐ - ☐**(S-####-#)** Visit date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)

Instructions for WHO Clinical Staging of HIV

[ptid] Participant ID ☐☐☐☐☐ - ☐**(S-####-#)** Visit date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)

Figures 2-4: WHO staging system for HIV infection in adults and adolescents > 13 years

Clinical Stage I

- Asymptomatic
- Persistent generalised lymphadenopathy (PGL)

Performance scale 1: Asymptomatic, normal activity

Clinical Stage II

- Weight loss, <10% of body weight
- Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
- Herpes zoster, within the last five years
- Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)

and/or performance scale 2: symptomatic, normal activity

Clinical Stage III

- Weight loss, >10% of body weight
- Unexplained chronic diarrhoea, > 1 month
- Unexplained prolonged fever (intermittent or constant) > 1 month
- Oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis, within the past year
- Severe bacterial infections

and/or performance scale 3: bedridden, < 50% of the day during the last month

Clinical Stage IV

- HIV wasting syndrome, as defined by CDC a
- *Pneumocystic carinii* pneumonia
- Toxoplasmosis of the brain
- Cryptosporidiosis with diarrhoea, > 1 month
- Cryptococcosis, extrapulmonary
- Cytomegalovirus (MCV) disease of an organ other than liver, spleen or lymph nodes
- Herpes simplex virus (HSV) infection, mucocutaneous >1 month, or visceral any duration
- Progressive multifocal leukoencephalopathy (PML)
- Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)
- Candidiasis of the oesophagus, trachea bronchi or lungs
- Atypical mycobacteriosis, disseminated
- Non-typhoid Salmonella septicaemia
- Extrapulmonary tuberculosis
- Lymphoma
- Kaposi's sarcoma (KS)
- HIV encephalopathy, as defined by CDC b

and/or performance scale 4: bedridden, < 50% of the day during the last month

a HIV wasting syndrome: Weight loss of > 10% of body weight, plus either unexplained chronic diarrhoea (> 1 month), or chronic weakness and unexplained prolonged fever (> 1 month).

b HIV encephalopathy: Clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings.

[ptid] Participant ID ☐☐☐☐☐ - ☐**(S-####-#)** Visit date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)

Inclusion Criteria

Items 1–6 must be answered "yes" for participant to be eligible.

		Yes	No
1	**[legage]** Is the participant of legal age to provide independent informed consent i.e. 18 years or older?	1	2
2	**[conct]** Was the participant willing and able to provide independent written informed consent for screening? *2a.* **[sgcon]** *When was the informed consent for screening signed or marked?* ☐☐ /☐☐☐ /☐☐	1	2
3	**[locator]** Was the participant willing and able to provide adequate locator information?	1	2
4	**[adh]** Is the participant willing and able to undergo clinical examinations, take study drug as directed for the specified period and adhere to the visit schedule?	1	2
5	**[contra]** Is the participant using a reliable method of contraception? *5a.* **[spcontra]** *Specify method of family planning here:* **TEXT**	1	2
	Items 6 is read aloud to the participant.	**Yes**	**No**
6	**[address]** Have you been staying at your current address for > one month?	1	2

[ptid] Participant ID ☐☐☐☐☐ - ☐**(S-####-#)** Visit date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)

Items 6–17 must be answered "no" for participant to be eligible

		Yes	No
7	**[stage34]** Does the participant have evidence of WHO Stage 3-4 disease?	1	2
8	**[coind]** Does the participant have any contra-indications to the use of acyclovir (epilepsy, kidney failure)?	1	2
	Items 8–17 are read aloud to the participant.	**Yes**	**No**
9	**[trial]** Are you currently enrolled in any other HIV treatment or prevention trial?	1	2
10	**[arv]** Are you currently taking any anti-HIV medicines (anti-retrovirals)	1	2
11	**[adv]** Have you ever had a known "bad" (adverse) reaction to acyclovir?	1	2
12	**[hepmed]** Are you currently taking any medicines such as acyclovir, valacyclovir, famciclovir, or foscarnet for the daily treatment of genital herpes?	1	2
13	**[gud]** Have you had a genital ulcer for more than one month which does not get better with treatment?	1	2
14	**[epigen]** Have you experienced > 6 episodes of genital herpes in the past year (twelve months)?	1	2
15	**[cpreg]** Are you currently pregnant or do you suspect that you might be pregnant?	1	2
17	**[tpreg]** Are you planning to become pregnant in the next four months?	1	2
18	**[travel]** Do you plan to travel out of the study area for more than two weeks in a row while enrolled in the trial?	1	2

[ptid] Participant ID ☐☐☐☐☐ - ☐**(S-####-#)** Visit date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)

→*Note that **Final Eligibility** is determined once Screening Laboratory Results Form (SLR) is completed.*

1	**[hivd]** HIV specimen collection date ☐☐/☐☐☐/☐☐ **(dd/mmm/yy)** **[inhiv]** HIV specimen collection date **0=Not apply 1. Apply** → *If no proof of test results available, perform rapid test to confirm status*		
2	**[hivst]** HIV status	**Positive = 1** **Negative = 2**	→**Ineligible**

3	**[hsvd]** HSV-2 specimen collection date ☐☐/☐☐☐/☐☐ (dd/mmm/yy) **[inhsv]** Incompleted HSV-2 specimen collection date **0=Not apply 1. Apply**		
4	**[hsvind]** HSV-2 index	☐☐.☐	If >3.4 go to item 6 If 1.1-3.4 go to item 5 **If <1.1 ineligible**
5	**[kalon]** Kalon HSV-2 EIA Resolve equivocal results	**Positive = 1** **Negative = 2** **Not done = 9**	→Go to item 6 →**Ineligible**

	(Index 1.1-3.4)		

6	**[urined]** Urine specimen collection date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)		
7	**[pregt]** Pregnancy test result	**Positive = 1** **Negative = 2**	**→Ineligible**
8	**[scrlysis]** Urinalysis	**Protein 3+ = 1** **<Protein 3+ = 2**	**→Ineligible**

9	**[cd4d]** CD4+ specimen collection date ☐☐/☐☐☐/☐☐ (dd/mmm/yy) **[incd4]** Incomplete $CD4^+$ specimen collection date. **0=Not apply 1. Apply**		
10	**[cd4c]** CD4 count	☐☐☐☐/µl	**→ If < 250, ineligible**
11	**[cd4p]** CD4 Percent	☐☐.☐☐ %	

Appendix E.2 ETHICAL CLEARANCE FROM ETHICS COMMITTEE.

[ptid] Participant ID ☐☐☐☐☐ - ☐**(S-####-#)** Visit date ☐☐/☐☐☐/☐☐ (dd/mmm/yy)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Horumpende

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M080339**
PROJECT	An analysis of clinical signs and symptoms which best predict the need for HAART initiation in HIV infected South African women
INVESTIGATORS	Dr P Horumpende
DEPARTMENT	School of Public Health
DATE CONSIDERED	08.03.25
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 08.04.07 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr S Delany-Moretlwe

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