SURVEY ON NAIL DISCOLORATION AND ASSOCIATION WITH CD4 COUNT AMONG UNTREATED HIV PATIENTS AT APIN CENTRE, NIGERIA

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A mini-thesis submitted in partial fulfillment of the requirements for the degree of Masters in Public Health at the School of Public Health,

University of the Western Cape

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SURVEY ON NAIL DISCOLORATION AND ASSOCIATION WITH CD4 COUNT AMONG UNTREATED HIV PATIENTS AT APIN CENTRE, NIGERIA

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KEYWORDS

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Cluster Differentiation of Antigen 4

Antiretroviral therapy

Nail Discoloration

WHO HIV Staging

Alternative Criteria

Screening tool

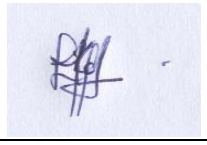
Dyschromonychia

Resource-Limited-Setting (RLS)

DECLARATION

I declare that "***Survey on Nail Discoloration and Association with CD4 Count among Untreated HIV patients at APIN Centre Jos, Nigeria"*** is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Peter Nnamdi Ekeh November 2010



Signed:_____

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LIST OF ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
APIN	AIDS Prevention Initiative in Nigeria
ART	Anti-retroviral therapy
ARV	Anti-retroviral drugs
CD4	Cluster of Differentiation antigen 4
CDC	Centres for Disease Control and Prevention, Atlanta, Georgia, USA
DCO	Dyschromonychia
FGN	Federal Government of Nigeria (Nigeria)
FMOH	Federal Ministry of Health
FN	False Negative
FP	False positive
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
JUTH	Jos University Teaching Hospital
NACA	National Agency for the Control of AIDS

ND	Nail Discoloration
NPC	National Population Commission
ND	Nail Discoloration
PHC	Primary Health Centre
PLWHA	People Living With HIV AIDS
PEPFAR	President Emergency Plan for AIDS Relief
PMTCT	Prevention of Mother to Child Transmission
SOPH	School of Public Health (University of the Western Cape)
TP	True Positive
TN	True Negative
UNAIDS	Joint United Nation Programme on HIV/AIDS
USG	United State Government
UWC	University of the Western Cape
VHCT	Voluntary HIV Counselling and Testing
WHO	World Health Organisation

DEFINITION IN TERMS:

Chi-square test: Statistical test used to test the null hypothesis that proportions are equal or that factors or characteristics are independent or not associated **(**Dawson & Trapp, 1994).

Confidence Interval: Gives a range of parameter values considered plausible for the population, based on the sample data, and is a useful way of describing the precision of the estimate (Katzenellenbogen, Joubert & Abdookarim, 1997).

Confounding variable: A variable more likely to be present in one group of subjects than another that is related to the outcome of interest and thus potentially confuses or *confounds* the results (Dawson & Trapp, 1994).

Cluster of differentiation antigen 4 (CD4): Is the T lymphocyte antigen receptor component and human immunodeficiency virus co receptor, is down-modulated when cells are activated by antigen (Pitcher, Honing, Fingerhut, Bowers & Marsh, 1999).

Independent Variable: The explanatory or predictor variable in a study (Dawson & Trapp, 1994).

Negative Predictive Value (NPV): The probability of a person not having a disease when the result of a test is negative (Beaglehole, Bonita, & Kjellstrom, 2006)**.**

Mathematically expressed as:

$$Negative\ Predictive\ Value = \frac{True\ Negative}{False\ Negative + True\ Negative} x\ 100$$ #

Population: Members of a defined group you want to gather information and make conclusions about (Dawson & Trapp, 1994)

Prevalence: The number of existing cases (both new and old) of a disease in a given population in a geographical area at a specified point or period of time (Beaglehole, Bonita & Kjellstrom, 2006).

Mathematically, Prevalence rate is expressed as:

$$Prevalence\ Rate = \frac{Total\ Number\ of\ cases\ of\ a\ disease\ (both\ new\ and\ old)\ at\ a\ specified\ time}{Population\ at\ risk\ at\ the\ specified\ time} x100$$

Positive Predictive Value (PPV): Is the probability of a disease in a patient with abnormal test result or person with a positive test has the disease (Beaglehole, Bonita & Kjellstrom, 2006).

Mathematically expressed as:

$$Positive\ Predictive\ Value = \frac{True\ Positive}{True\ Positive + False\ Positive} x100$$

P-value: Is the probability of finding an association or a difference, if there is in reality no association or no difference (Katzenellenbogen, Joubert & Abdookarim, 1997)

Reliability: The observer (or someone else doing the test) repeating the test using same method should be able to obtain the same findings (WHO, 2001).

Relative Risk (R.R): The ratio of the incidence of a given disease in exposed or at risk persons to the incidence of the disease in unexposed persons (Dawson & Trapp, 1994). R.R greater than 1(one) shows an association between the risk (CD4 count ≤200cells/mm^3) and the disease (ND). R.R=1 no association and R.R less than 1 shows the risk factor is protective.

Relative Risk is expressed as:

$$Relative\ Risk = \frac{disease\ risk\ in\ the\ exposed}{disease\ risk\ in\ the\ non-exposed}$$

Sample: Sub-set of the entire population (Katzenellenbogen, Joubert & Karim, 1997)

Statistics: A summary number for a sample, often used as an estimate of a parameter in the population (Dawson & Trapp, 1994)

Standard Deviation (SD): The most common measure of dispersion or spread, it can be used with the mean to describe the distribution or spread. It is the square root of the average of the squared deviations of the observations from their mean (Dawson & Trapp, 1994)

Sensitivity: The probability of a positive test result in patients who have the condition (*positivity in disease*) (Dawson & Trapp, 1994).

Mathematically expressed as:

$$Sensitivity = \frac{True\ Positive}{True\ Positive + False\ Negative} x\ 100$$

Specificity: The probability of a negative test results in patients who do not have the condition or the proportion of patients without the condition who test negative (Dawson & Trapp, 1994).

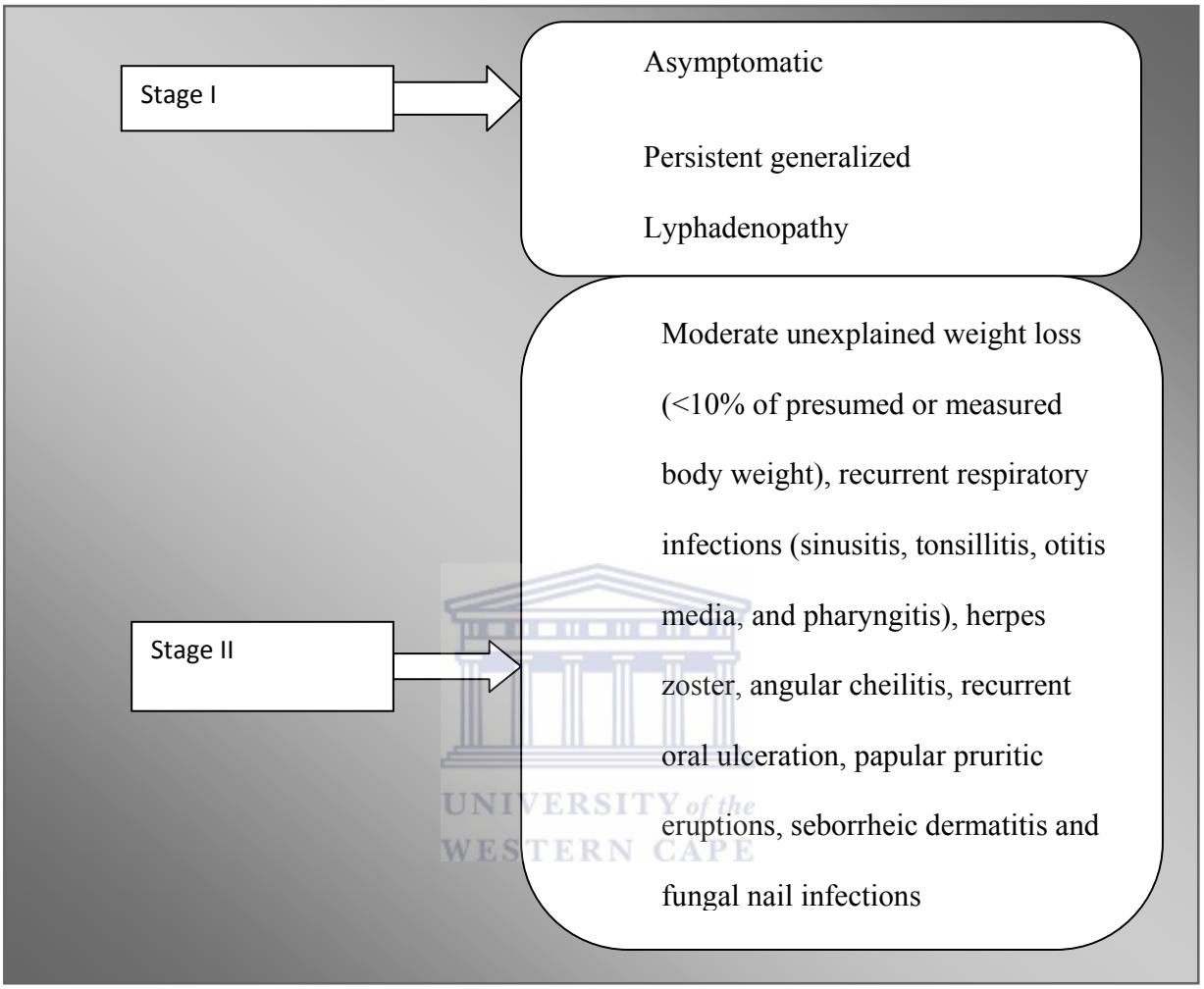
Mathematically expressed as:

$$Specificity = \frac{True\ Negative}{False\ Positive + True\ Negative} x\ 100$$

Variables: Is the characteristics which one measures, and about which data are collected, it can be Categorical or Numerical (Katzenellenbogen, Joubert & Abdookarim, 1997).

Validity: Means that the measurement should actually represent what it is intended to measure (WHO, 2001).

WHO Clinical Stage 1 & II of HIV/AIDS for Adults and Adolescents (PEPFAR, 2009**):**



ABSTRACT

Survey on nail discoloration (ND) and association with CD4 count among untreated HIV patients APIN Centre Jos, Nigeria

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Background: Eligibility for antiretroviral therapy (ART) in HIV-infected patients is defined either by a cluster of differentiation antigen 4 (CD4) count of less than 200cells/mm^3 or clinical diagnosis of WHO stage III and IV. Therefore, the decision to start ART becomes difficult when CD4 cell count is not available. With limited laboratory infrastructure, the decision to start ART is usually made based on clinical symptoms leading to late commencement of ART. This calls for alternative criteria to see if nail discoloration (ND) correlates with low CD4 count among untreated HIV infected patients. This will serve as a complementary screening tool for identifying asymptomatic ARV naive HIV patients with a CD4 cell count of less than 200cells/mm^3 which signifies severe immunosuppression.

Study Design and Setting: This was a quantitative cross-sectional descriptive and analytical study involving adult ART naïve HIV infected patients in WHO stage I and II. Systematic sampling was used to select the participants from all adult ART naïve HIV infected patients attending APIN clinic, located at the Jos University Teaching Hospital (JUTH), Jos, Nigeria.

Data Collection: Face-to-face interviews, physical examination and relevant laboratory investigations with selected participants were conducted using a questionnaire guide. Questions on socio-demographic characteristics, clinical data, general physical examinations including finger nail examination and photographing with subsequent laboratory investigations including CD4 count and western blot were employed.

Data Analysis: Variables were categorized and data analyzed using descriptive statistics including the frequency, percentage frequency; mean and standard deviation of continuous variables. Association between CD4 count of ≤200cells/mm^3 and ND was tested using the chi-square test with an alpha level of 0.05. Prevalence of ND, sensitivity, specificity, positive predictive and negative predictive values and accuracy of the screening test of ND was calculated.

Results: 394 patients had their fingernails photographed and assessed. It was shown that distal banded and grey nails were the common types of ND seen with a prevalence of 38%. There was an association between CD4 count ≤200cells/mm^3 and ND ($p<0.0001$). CD4 count ≤200cells/mm^3 was a risk factor for developing ND (RR=2.3[1.8-3.6]). The association has a sensitivity of 78%, specificity of 55%, positive predictive value of 50%, and negative predictive value of 80% and accuracy of test 63%.

Conclusion: With a significant association ($p<0.0001$) and a sensitivity of 78%, ND can be a useful clinical indicator of immune dysfunction mediated by HIV among patients in WHO stage I or II. ND can either be a clinical sign or a symptom in HIV patients with a CD4 of ≤ 200cells/mm^3 as seen in the study as the specificity and sensitivity of ND compared favourably with other WHO stage III diagnosis.

Recommendations: Nail discoloration should complement CD4 count as an additional staging sign to help identify patients likely to benefit from ART especially in resource-limited settings. Finally, all patients with grey or distal banded should be on co-trimoxaxole prophylaxis in line with WHO /national guideline on the use of co-trimoxaxole for all HIV positive patients with a CD4 cell count of ≤350cells/mm^3.

CHAPTER 1

INTRODUCTION

1.1. Background

Since the first case of Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) was reported in Nigeria in 1986 (Abdusalam & Tekena, 2006), the number of people living with the virus has steadily increased. Nigeria has a HIV prevalence of 4.6% (NACA, 2010). HIV/AIDS associated mortality and morbidity have continued to rise in spite of the efforts of the Federal Government of Nigeria (FGN) and international and local partners to combat the disease and HIV/AIDS continues to be a major public health concern for the country. It was estimated that in 2009, the annual AIDS deaths was 192,000 (male: 86.178; female: 105,822) (NACA, 2010). These deaths due to HIV/AIDS, has increased the number of orphans and decreased the size of the workforce as it affects mainly adults in their most productive years of life (15-49 years) (FMOH, 2005). The rate of HIV infection continues to rise with 336,379 new infections recorded in 2009, while an estimated number of about 2.98 million people live with HIV/AIDS (NACA, 2010). In response to this challenge, the FGN, as part of its care and support strategy to combat HIV/AIDS, initiated the National Antiretroviral Drug Access Programme to improve the health and quality of life of People Living with HIV/AIDS (PLWHA) in Nigeria. The FGN also developed national ART guidelines which serve as a tool to equip clinicians to manage patients appropriately in all the tiers of the healthcare delivery system (FMOH, 2006). According to the National Agency for the Control of AIDS (NACA), about 100,000 PLWHA who met the eligibility criteria were on ART in Nigeria as of December 2006 (UNICEF, 2007). This number is far below the number of people who should be on ART.

According to NACA, 857,455 (adult 754,375; children103, 080) require ART (NACA, 2010) but were denied access because they did not meet the eligibility criteria (Onwujekwe, 2010).

The eligibility criteria to determine those in need of ART initiation in Nigeria, is the same as the WHO criteria (Table 1) and is defined as WHO Stage I or II with CD4 count of less than 200cells/mm^3; WHO stage III disease with CD4 cell count of less than 350cells/mm^3 or WHO stage IV disease irrespective of the CD4 count (FMOH, 2005). In December 2009, the World health organization (WHO) updated its guidelines for the commencement of ART for adults and adolescents (WHO, 2010). Nigeria is yet to incorporate these guidelines into her ART treatment protocol but promised to do so (Personal Communication: Dr Ernest Ekong, APIN Plus/Harvard PEPFAR Nigeria Clinical Coordinator, 19th May 2010). According to the new ART guidelines, all adolescents and adults including pregnant women with HIV infection and CD4 counts ≤ 350 cells/mm^3 should be started on ART regardless of whether they have clinical symptoms (WHO, 2010). These Nigeria/WHO criteria require laboratory assessment in order to decide ART eligibility. CD4 count is important in the WHO HIV clinical staging system as both clinical classification system and a laboratory CD4 cell count classification are used to categorize patients. CD4 count assessment has been a major challenge that prevents people from accessing ARV's and care from reaching many more in need, especially in rural settings where low cost ARV are now being offered with CD4 machine unavailable for routine use (USAID,2008). High-quality treatment, care and prevention programs depend on effective and reliable laboratory infrastructure (Abimiku, 2009). Where these laboratory infrastructures are present, the cost of services becomes an obstacle to its use for the majority of those in need. In areas with limited laboratory infrastructure, the decision to start ART is often made based on clinical symptoms, which means that ARVs are commenced too late for the patients to derive maximum benefit.

The timely initiation of ART at WHO Stage I or II disease with CD4 cell counts of less than 200cells/mm^3 has been found to increase physicians confidence that mortality and morbidity rates due to progression to advanced HIV are reduced with ART (Lawn, Harries, Anglaret, Myer & Wood, 2008; Wolbers *et al.,* 2008). In addition, it decreases expenses for palliative care and decreases the number of orphans as mortality from advanced AIDS is avoided (Lawn *et al.,* 2008; Alcorn & Safreed, 2009).

Until CD4 cell count testing becomes universally accessible, there is an urgent need to identify alternative markers of disease progression, which will assist in the identification of patients with WHO stage I or II diseases with CD4 cell counts less than 200cells/mm^3 in resource limited settings. Nail discoloration (ND) is proposed to be one of such marker. If correlation exists between ND and CD4 count of less than 200cells/mm^3, it will serve as an alternative marker of disease progression and will help in identifying those who are eligible for ART. Identifying alternative markers of disease progression is in line with WHO affirmation that all national and international health policies be based on valid scientific evidence (Fathalla, 2004).

Table 1: WHO eligibility criteria for commencement of ART

WHO Clinical Staging Definitions	CD4 counts(cells/mm^3)	ART Eligibility
Stage 1	<200	Eligible
Asymptomatic		
	>200	Not eligible
Persistent generalized lymphadenopathy		
Stage II	<200	Eligible
Moderate unexplained weight loss (<10% of Presumed or measured body weight.		
Recurrent respiratory infections.		
	>200	Not eligible
Herpes zoster		
Angular cheilitis		
Recurrent oral ulcerations		
Popular pruritic eruptions		
Seborrheic dermatitis		
Fungal nail infections		
Stage III	< 350	Eligible
unexplained severe weight loss(>10% of presumed or measured body weight)	>350	Not eligible
unexplained chronic diarrhea for >1 month		
unexplained persistent fever for >1month		
persistent oral candidiasis (thrush)		
oral hairy leukoplakia		
pulmonary tuberculosis (current)		
severe presumed bacterial infections		
acute necrotizing ulcerative steatites, gingivitis or periodontitis		
unexplained anaemia(haemoglobin <8 g/dl)		
neutrophils <500cells/mL)		
chronic thrombocytopenia (platelets <50,000cells/mL)		

Stage IV	Eligible irrespective of CD4 count
HIV wasting syndrome	
Pneumocystis pneumonia Recurrent severe bacterial pneumonia	
Chronic herpes simples infection	
Candidiasis of esophagus, trachea, bronchi or lungs	
Extra pulmonary tuberculosis	
Kaposi sarcoma	
Cytomegalovirus infections	
Central nervous system toxoplasmosis HIV encephalopathy e.t.c	

Source: PEPFAR/Harvard School of Public Health, Adult Antiretroviral Treatment Protocol version 2.0, 2009.

1.2. Problem Statement and Study Rationale

Most physicians working in APIN clinic, JUTH had observed that several HIV infected patients in WHO stage I or II presented to the adult ART clinic with ND. During physical examination it was found that the nail colours were grey, half and half grey or blue or distal banded nails. These observations, led to the comparison of these nail features with the patients CD4 count level and it was found that several patients had a low CD4 less than 200cells/mm^3.

This observation served as the motivating factor for conducting this research. This research would complement CD4 count testing which was a necessary diagnostic tool in determining the eligibility criteria for the commencement of ARV's. Factors ranging from other medical conditions, trauma and local nail dye application could influence the cause of ND among HIV patients. Patient's history, physical examinations and relevant laboratory investigations would help in associating its correlation with HIV and low immunity. That meant that all HIV infected patients would be examined for ND and CD4 count tested for possible association while other factors that could cause ND could be ruled out. If correlation exists and a screening tool is created, it would help to reduce the number of HIV patients presenting in WHO stage III and IV and also the burden associated with their management. It would save cost in the management of HIV patients who could not afford the cost of travelling to urban areas for a CD4 count testing. Finally the difficulty encountered in taking blood samples from the rural areas to urban areas for CD4 count testing will be reduced.

1.3. Description of Research Setting

This research was carried out at the Harvard/U.S President Emergency Plan for AIDS Relief (PEPFAR)/APIN Clinic, Jos University Teaching Hospital (JUTH) Jos, Plateau State,

North Central Nigeria. It is a tertiary, referral hospital serving six states (Plateau, Nasarawa, Benue, Bauchi, Taraba and Gombe) with a total population of 18,592,311 (NPC, 2006).These states are made up of different ethnic groups. Hausa is the common language spoken and the major ethnic group. The clinic is one of the major sites where the free ART programme of the United States government through the APIN/Harvard PEPFAR is being implemented in Nigeria and has 19,000 patients with Male:Female ratio approximately 1:2, in its care as at October 2009 (Personal Communication: Dr Patricia Agaba, APIN Site Coordinator,11th November 2009).

The economic base of the majority of the people that patronize the clinic is farming; while civil servants, the military, paramilitary, business community and petty trading make up a small proportion of other users. All of its services (drugs, laboratory and clinical) are free. The laboratory is presently undergoing Centre for Disease Control and Prevention (CDC) assessment in preparation for WHO accreditation (Personal communication: Mr. Godwin Imade, APIN Laboratory Manager, 20th May 2010). It is the only laboratory within the north central zone fully equipped by PEPFAR for effective management of HIV/AIDS and research (Personal communication: Mr. Godwin Imade, APIN Laboratory Manager, 20th May 2010). The laboratory was staffed with trained laboratory scientist and carried out all necessary investigations required for the effective management of HIV. HIV services are being scaled-out to secondary and primary health care institutions together with laboratory services. The programme has three clinics, the pediatrics, maternity (PMTCT) and the adult antiretroviral units.

1.4. Study Objectives

1.4.1. Aim

To investigate the prevalence of nail discoloration among untreated HIV infected patients, its association with CD4 cell count and its potential For use as an indicator for the initiation of ART

1.4.2. Specific Objectives

1. To determine the prevalence of nail discoloration among untreated HIV infected patients presenting at the APIN clinic, Jos University Teaching Hospital.
2. To characterize the type of nail association in untreated HIV infected patients presenting to the APIN clinic at the Jos University Teaching Hospital, Nigeria.
3. To determine the Positive Predictive Values (PPV), sensitivity and specificity of nail discoloration with CD4 levels.

CHAPTER 2

LITERATURE REVIEW

2.1. Anatomy of the Nail

Anatomically fingernails are made up of a tough protein called keratin and have many different parts, namely: cuticle, nail plate, nail fold, lunula and nail bed (Fig.1). Among the important parts are the nail plate and the lunula. The nail plate is the hard and translucent portion, composed of keratin underlined by a pink nail bed which is due to its rich vascular network (DermWeb, 2009), while the lunula is the crescent shaped whitish area of the nail bed. Functions of the fingernails include: Protecting the distal phalanx from trauma, helps in picking up small objects, aids in the appreciation of fine touch, used for scratching and aesthetic organ.

The growth of the nails is continuous throughout life and it is 0.5 to 1.2mm per week (Derm Web, 2009). The nail color changes are classified according to whether these occur in morphology (shape) or color of the nail (Gregorion, Argyrion, Larios & Rigopoulos, 2008).

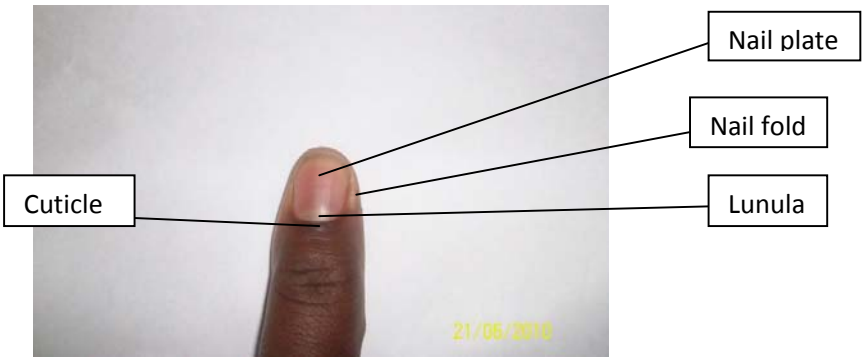

Figure1: Normal fingernail

2.2. Causes of Nail Discoloration

The nail is part of the skin but it is not located in the dermis but in the fingers and toes (Choi, 2002), so nail discoloration is a skin disorder. Daniel (1985) summarized the causes of nail discoloration into four different categories of pigmentation abnormalities:

1. Changes attributable to other systemic diseases. These include diseases that involve organs which can cause changes in the nails as well. For example kidney failure, cirrhosis of the liver and HIV infection.
2. Changes caused by systemic drugs or ingestants. Different drugs or ingestants can lead to discoloration of nails, which usually gets better after the drug is stopped. For example blenoxane, chloroquin, minocycline, Highly Active Antiretroviral Therapy (HAART) like zidovudine, entricitabine and severe arsenic poisoning (Levay, Botes & Malela, 2005).
3. Changes attributable to local agents such as nail dyes and other topical agents.

4. Changes attributable to some nail entities. People with separation of the nail plate from the nail bed or complete nail plate loss are at risk of infection with fungus leading to ND.

It is increasingly acknowledged that the nail and systemic diseases are interconnected and that nails can provide valuable diagnostic or screening clues to underlying pathologic conditions, such as HIV and AIDS (Daniel, 1985; Starrianeas *et al.,* 1993 & Gregorian *et al.,* 2008). Nail changes are classified according to morphology or color of the nail (Gregorion *et al.,* 2008).

Scarborough *et al.* (2006) and Gregorion *et al.* (2008), described distal banded nail as a situation where most of the nail plate is white, with a narrow pink or transverse band of darker than normal nail pigmentation of 1 to 3mm in width in the distal nail bed. All the nails tend to be uniformly affected. This type of nail is sometimes referred to as half and half nails where the proximal portion of the nail bed is whitish because of edema of the nail bed and capillary network; distal portion is pink and reddish brown. The nail plate of the patient is unaffected. This type of nail disorder is found in patients with HIV infection and among patients with cirrhosis of the liver, chronic congestive heart failure, haemodialysis and renal transplant recipients (Gregorion *et al.*, 2008).

Other conditions like heart failure may cause pink nails, while yellow nails may result from lymphatic obstructions and white nails may suggest a chronic liver disease or renal failure (Rehmus, 2007). Grey nail has also been shown to result from HIV infection (Scarborough *et al.,* 2006).

Longitudinal pigmented bands on the nail (brown-black nail) can be found in 77% of people of the black race (Woo & Sibbard, 2007). These bands are regular and extend from the proximal nail fold to the distal tip of the nail. Transverse lines on the nail occur in 7.1% of cases, while leukonychia or white nails (white discoloration appearing on nails) occur in 14.3% of

cases and longitudinal melanochia occur in 14.8% of cases of untreated HIV patients (Cribier *et al.,* 1998). Bluish or grey color of the nail bed is said to have a prevalence of 19% among untreated HIV patients (Levay, Botes & Malela, 2005). These nail color changes has been a useful tool in determining CD4 count level as these studies (Panwaker, 1987; Cribier *et al.,* 1998; Levay, Botes & Malela, 2005, Woo and Sibbard, 2007 & Namakoola *et al.*, 2010) correlated them with immunosuppression. Other causes of nail color changes include; chemotherapy such as blenoxane, silver, minocycline; severe arsenic poisoning, zidovudin, drug hypersensitivity reaction such as tetracycline and fluconazole. Diseases/infections like Plummer-Vinson syndrome, iron deficiency anemia, fungal and pseudomonas infection, atopic dermatitis, jaundice, lichen planus, psoriasis, yellow nail syndrome, onycholysis, senile ischemia, malnutrition and chronic lung disease are also known causes of ND (Rehmus, 2007). These diseases or infections causing ND are common among HIV patients in WHO stage III and IV (table 1). Tobacco use and trauma have also been linked to cause ND (Gregorion *et al.,* 2008).

2.3. Nail Discoloration, Human Immunodeficiency Virus and Cluster Differentiation of Antigen 4 Count

Skin disorders are commonly encountered in HIV infected patients and may be the first manifestation of HIV disease. This skin is more likely to have an unusual appearance among those with advanced AIDS (Tse, 2007). Up to 90% of HIV infected persons suffer from skin diseases during the course of their illness. Out of these, nail disorders constitute up to 10% and are more prevalent in the elderly (Woo & Sibbald, 2007). Factors like immune depression and concurrent use of HAART have led to the high prevalence of skin disorders (Personal communication: Dr Ekpudu Violet, Consultant Dermatologist, and 10th March 2009). Others

include the pattern of endemic infections, impaired circulation and concurrent chronic illness such as Diabetes Mellitus (Glaser & Remlinger, 1996). The prevalence of skin diseases may vary with one's geographic location (Tse, 2007). Infection with HIV leads to a chronic and, without treatment, usually fatal infection characterized by progressive immunodeficiency with or without long clinical latency period and associated opportunistic infections. The hallmark of HIV disease is infection and viral replication within T- lymphocytes expressing the CD4 antigen (Sax, Cohen & Kuritzkes, 2010). Cell mediated response are of two types, the CD4 cells (helper cells as it activates and coordinates other cells of the immune system) and the CD8 (suppressor cells) which destroys cells infected by bacteria and viruses.

CD4 cells are a critical component of normal cell mediated immunity. The CD4 cell is an indication of the T-helper cells in the blood and is a subset of the lymphocytes which gives a reflection of the strength and weakness of the immune system in the body and a predictor of the rate of development of opportunistic infection in the body. A report in Nigeria has found CD4 cell counts in healthy Nigerians to range from 636cells/mm^3 to 977cells/mm^3 (Olaleye, Harry & Odaibo, 2006). Once in the body, HIV attaches to helper T-lymphocytes whose surface has a receptor called CD4 which enables HIV to attach to them. Inside this CD4 cells, HIV uses the lymphocytes' own genetic machinery to reproduce itself leading to the destruction of the lymphocytes and subsequent weakening of the body's immune system which protects against infections and cancers. Without treatment, the average time for acquisition of HIV to an AIDS-defining opportunistic infection in 90% of people infected with HIV is less than 10 years (Sax, Cohen & Kuritzkes, 2010; Lynen, 2008). Individual variability in these time intervals exists as some patients may progress from acute HIV infection to death within 1-2 years and some for

greater than 10 years (Sax, Cohen & Kuritzkes, 2010). One of the steps to a successful ART is to diagnose and treat before the immune system is severely suppressed.

There has been limited research on CD4 count correlation with ND and these studies correlated ND with immunosuppression (Cribier *et al.,* 1998; Levay, Botes & Malela, 2005; Scaborough *et al*., 2006; Woo & Sibbard, 2007; Namakoola *et al.*, 2010). No similar study about this correlation has been conducted in Nigeria, although on the African continent (Malawi, South Africa and Uganda), similar studies have been conducted (Levay, Botes & Malela, 2005; Scaborough *et al*., 2006; Namakoola *et al.*, 2010) and screening tool developed (Scaborough *et al*., 2006).

Scaborough *et al.* (2006) reported the relationship between ND in HIV untreated patients and their level of CD4 cell count in a cross-sectional study in Malawi. A total of 222 patients with a mean age of 34.2 years participated in the study and had all their nails photographed. Grey or distal banded nails were significant ($p<0.0001$) and when compared with the control (pink nails), grey or distal banded nails was strongly associated with a CD4 count of less than 200cells/mm^3 (Scaborough *et al.,* 2006). The sensitivity was 56%, specificity of 85% and a positive predictive value of 81%. The researchers concluded with a recommendation for clinicians working in sub-Saharan Africa without access to CD4 cell count testing, that grey or distal banded nails represent an additional staging sign to help identify a subgroup likely to benefit from ART without access to CD4 count (Scaborough *et al.,* 2006). Though the sensitivity was low (56%), the researcher argued that it is so with all clinical markers of HIV progression. The study produced a classification system for ND (screening tool) as part of recommendations for use by clinicians working in sub-Saharan Africa without access to CD4 cell count testing. The study did not produce prevalence for ND and did not mention how confounders such as age

and sex were controlled for and how they were able to arrive at "normal" or "grey/distal banded" nails. Since what was described as "grey/distal banded" nails could be a normal nail for that patient who must have had it prior to contacting HIV infection.

Namakoola *et al.*, (2010) in a cross-sectional study was able to establish the association between grey/distal banded nails and immunosuppression when he evaluated the use of grey/distal banded nails as an indicator of advanced immunosuppression, and thus eligibility for ART, in resource poor settings. He found that grey/distal banded nails were significantly associated with a CD4 count of ≤200cells/mm^3 (P<0.001) but no association with CD4 count of cut-off of ≤350cells/mm^3.Because of the low sensitivity (66%), the study did not recommend the use of grey/distal banded nails as a tool to a guide ART initiation; as large number of patients eligible for ART will be missed. The results also had a specificity of 50% and a negative predictive value of 77%.

Levay, Botes & Malela (2005) defined Dyschromonychia (DCO) as the total absence of the nail lunula with the presence of a bluish-grey discoloration of the nail or nail bed. It is a term generally applied to patients with increased nail pigmentation. A form of ND, DCO was found to be associated with HIV in a study that was to determine the association with HIV and DCO (Levay, Botes & Malela, 2005). This study had a hypothesis that DCO was a predictor of advance immunosuppression in HIV disease and was carried out at the immunology clinic. It was a prospective observational study. A hundred consecutive clinic patients were evaluated by three doctors. The prevalence of DCO was 19% at the immunology clinic and 52% (probably due the advanced HIV/AIDS infection) for those admitted in the ward with associated immunosuppression (Levay, Botes & Malela, 2005). All the finger nails were equally affected in 7.25% of cases but the nails involved most commonly were the thumb and the ring finger

(Levay, Botes & Malela, 2005).With this prevalence, they concluded that there was a close association between HIV and DCO in the case of low CD4 count and that the presence of DCO has a high sensitivity for HIV sero-positivity otherwise serving as a screening tool. That the clinical findings of DCO is simple, quick and efficient sign for the evaluation of the immune status of HIV population with reasonable sensitivity (66%) and specificity (92%) for low CD4 count (Levay, Botes & Malela, 2005). Considering the study design used (prospective study), patients were supposed to be followed when there were no DCO and observed when they start having DCO. This perhaps would have taken a longer time. This study design was not supposed to give us the prevalence of DCO. These patients were chosen at a particular point in time at the clinic and the ward with a prevalence of DCO, these indicates that it was a cross sectional study. If the original study design was followed, these would have helped to determine the precise risk factor, even though it was expensive and time consuming. On the use of three doctors for evaluation of the patient with DCO, the study did not address the method of DCO identification as determining DCO is subjective and thus will increase the rate of measurement bias.

Cribier *et al.* (1998) in a prospective cohort study carried out in an HIV care centre, France to study the frequency of nail changes in a population of HIV infected patients examined and photographed all the patients' nails. A total of 155 untreated HIV-1 positive and 103 healthy HIV negative controls were recruited. Out of these, ND was present in 67.7% of HIV positive patients and was linked with immunosuppression (Cribier *et al.,* 1998). Results show nail symptoms of transverse lines (7.1%) and longitudinal melanochia (14.8%) more frequent among the HIV positive group than healthy controls (Cribier *et al.,* 1998). The study did not correlate the ND with the level of CD4 cell count like Levay, Botes & Malela (2005) and did not mention how the sample number and selection was made. Cribier *et al.* (1998) in his conclusion

emphasized a systematic nail examination of HIV infected patients and advocated for further studies correlating ND with levels of immunosuppression.

Rizos, Drosos & Ioannidis (2003) in their case report, observed that during physical examination in an untreated HIV patient in Greece, they found nail pigmentation with a CD4 cell count of 116 cells/mm^3 which they associated with HIV following patients history and laboratory investigations they conducted. This report was descriptive in nature and could not describe the association between the pigmented nail and HIV. Nagalingeswaran *et al.* (2000) examined the type of dermatologic findings including nail changes present among HIV infected patients in an AIDS research and education centre in India. A total of 833 HIV patients were examined. Eighteen (18) untreated patients had black colored nails with varying degrees of immunosuppression present. The study could not give the degrees of immunosuppression present.

Many articles agreed that distal banded nails or half and half nails were associated with HIV (Gregorion, Argyrion, Larios & Rigopoulos, 2008; Chadrasekar, 1989). Beau's line, a form of ND, in association with pallor of the nail beds was said to be a general effect of chronic illness and has been associated with HIV and can serve as a pointer to severe immunosuppression (Erdal, Zalewska, Schwartz & Hamadeh 2007; Daniel, Norton & Scher, 1992; Pros, Abson, Scher, 2007). Also, nail color changes such as yellow discoloration of the distal part of the nails and hyper pigmentation showed a statistically significant correlation with HIV and immunosuppression (Sindrip, Lisby, Weismann & Wantzin 2007; Dover & Johnson, 1992; Smith *et al.*, 1994; Reynaud-Mendel *et al.*, 1996; Matis, *et al.,* 1987; Aftergut, 1999; See & Wong, 1992; Chernosky & Finley, 1985).

In conclusion various studies have correlated different types of ND with immunosuppression with significant findings (P<0.001) and recommendations were made. With prevalence of ND (distal banded, grey or DCO) in HIV infected patients ranged from 19% (Levay, Botes & Malela, 2005) to 67% (Cribier *et al.,* 1998). Scaborough *et al. (*2006), Namakoola *et al.* (2010) and Levay, Botes & Malela (2005) had ND sensitivity of 56%, 66% and 66% respectively. Sensitivity was for all the population with ND, these results were not too good, and that means that some people with ND were missing in the population. This does not mean that the sensitivity should be rejected as it is still better than a random guess. Specificity of 85% (Scaborough *et al.,* 2006) and 92% (Levay, Botes & Malela 2005) was looking at those population without ND and these figures suggested a good specificity. A positive predictive value of 81% (Scaborough *et al.,* 2006), though not too good but it was still better than chance as it only gave those with ND in the population. Population groups in Nigeria have not been previously assessed for association of ND with CD4 cell count. This study intends to investigate the prevalence of ND among untreated HIV patients and if HIV untreated patients with ND have an association with low CD4 cell counts.

CHAPTER 3

METHODOLOGY

3.1. Study type/design

The study was based on a quantitative cross-sectional descriptive and analytical study. It involved the description of types of ND among adult ART naïve HIV patients in a HIV clinic in Jos, Nigeria and analyses were carried out to identify if there was association of ND and low CD4 count.

3.2. Study population

The study population involved all ART naïve HIV infected adult patients in WHO stage I and II (Table1) attending the APIN clinic at JUTH, Jos in Nigeria. All study participants were 17 years of age and above. After applying exclusion criteria (those whose nails could not be evaluated due to trauma, dystrophy or nail polish and those patients already in WHO stages III & IV [see table1], histories of prior exposures to HAART), 394 patients remained to serve as the sampling frame (source population).

3.3. Sample size

The minimum sample size of 392 participants was calculated using Open Epi version 2.2.1 computer programme (Dean, Sullivan & Soe, 2009) assuming a significance level of 0.05, a hypothesized ND prevalence of 19% (Levay, Botes & Malela, 2005) with a total patients attendance of 19,000 since the inception of the clinic 5 years ago (APIN clinic record as at October, 2009). However to take care of refusal by some clients to participate, non-response or

incomplete data, questionnaire was administered to 439 participants who consented to research, clinical examination and laboratory investigations were evaluated done.

3.4. Sampling procedure

The clinic presently enrolls 0 to 18 new patient's daily (Clinic enrollment register from January to April 2010). After applying the exclusion criteria, 439 subjects were systematically selected from a population of 1260 who presented at the clinic from the 3rd May to 16th of July. The patients who presented daily for enrollment into the HIV treatment and care program had undergone a voluntary HIV screening at the APIN voluntary counseling and testing centre or were referred from other sites. At the APIN clinic, these patients were allowed to pass through the normal clinic enrollment procedures which involved obtaining hospital numbers, group post-test counseling on HIV, taking of vital signs and sorting of patients based on clinical presentation in order that those who were too sick were given urgent attention in line with the routine health services provision in the clinic.

After the normal clinic procedures, patients were taken to see the two doctors for pre-assessment which involved history-taking, clinical examination and laboratory evaluation. The pre-assessment level was the first contact of the patients with the investigator or interviewer. A random starting point from 1 and 1260 was selected in order to determine the starting point. With a sample interval of 3, every third person that presented to the investigator was selected until the required sample size was obtained. The two interviewers in their consulting rooms requested patients to participate in the study and interviewed them after they offered consent. Any patient with a visible exclusion criteria (WHO stages III and IV, painted, dystrophic or traumatic nails), was not requested to participate. Those with clinical findings (past histories of haemodialysis,

nail painting or smoking) and laboratory findings (negative Western blot, liver or kidney derangement, diabetes mellitus) with link to ND were regarded as indeterminate and excluded from analysis. Patient attrition was not anticipated in this study, since it was cross-sectional.

3.5. Data collection and processing

Data was collected through face-to-face interviews with patients who gave consent and met the inclusion criteria. Two medical doctors (who were part of the doctors involved in the pre-assessment of patients in the APIN clinic) who participated in the study were selected based on qualification, interest in participating in the research and the ability to use a camera. They were briefed on why the study was being conducted and trained on how to use the digital camera for taking clear photos and on how to administer the questionnaire. The student investigator did not take part in data collection in order to ensure that bias was not introduced. A structured questionnaire (Appendix 3) was administered by the clinicians. The questionnaire contained two parts (sections A and B). Section A captured the patient's demographic profile. While section B captured the patient's medical history including their current health and medication, physical examination findings and laboratory investigations such as CD4 count and Western blot for HIV infection confirmation. As the patients present to the clinic, their fingernails were photographed after hand washing with antiseptic soap and water using a bright indoor daylight with a digital still camera by the trained clinicians. All photographed nails were passed round to four selected clinicians (blinded to patient identity) in APIN clinic for identification of various nail colors using the nail color chart produced by Scaborough *et al*., 2006.

. These clinicians (could be doctor, nurse, pharmacist or a counselor) had their names written on a piece of paper and were randomly handpicked. All the four clinicians agreed that

normal nail color and ND (grey or distal banded) existed 394 clients. Other inconclusive findings (dystrophic, nail polish, smokers, laboratory findings suggestive liver, renal disease or diabetes mellitus linked to ND or a negative western blot result, poor photographing[early part of the study when the use of the camera had not been mastered] and discordant nails colors among clinicians) was also recorded as indeterminate (Fig.2-4) and excluded from the final data analysis. Nail colors were recorded as pink (normal), distal banded, grey or indeterminate nails. Information from the questionnaire was entered into an Epi info 3.5.1 database (CDC, Atlanta, Georgia, USA) for analysis.

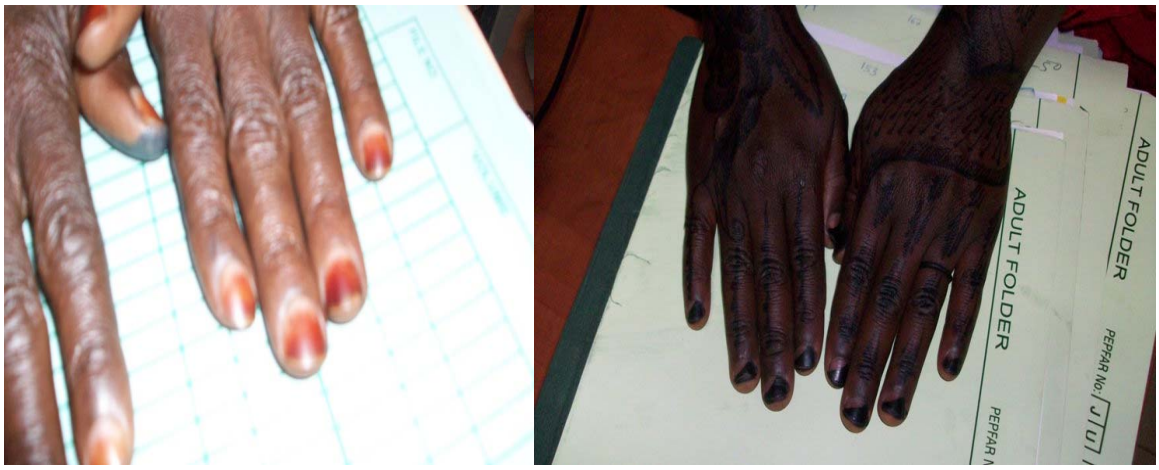

Figure 2: Indeterminate (painted) nails. Painted nails due to cosmetics (left) and local nail paints (right)

Figure 3: Indeterminate (infected) nails. Infected nails with abnormal nail plate and bed.

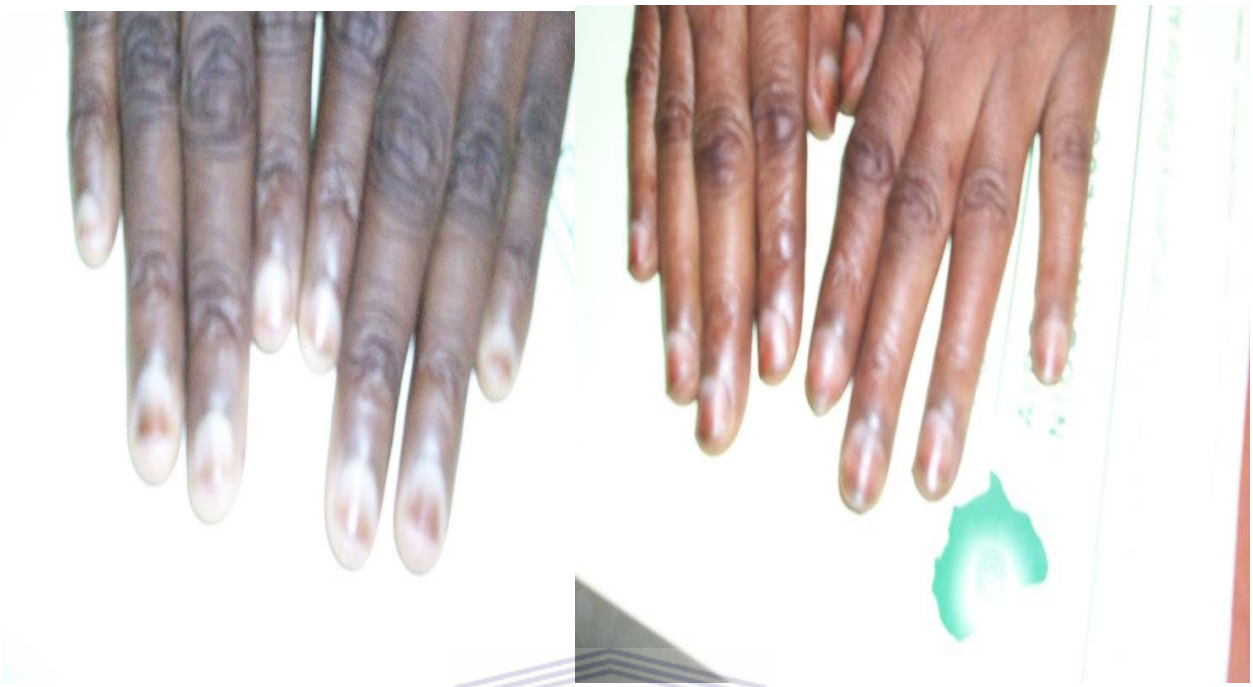

Figure 4: Indeterminate nail (poor photographing). Distal banded nails with poor photographing

3.6. Validity

A study can be said to be valid if its results corresponds to the truth (Beaglehole, Bonita & Kjellstrom, 2006). To ensure validity, sample size was calculated with a required level of statistical significance of the ability to detect a difference, the amount of the disease in the population and the size of the group being compared using Open Epi version 2.2.1 computer programme (Dean, Sullivan & Soe, 2009). Systematic sampling was used to obtain the sample size from the sampling frame in order to reduce selection of participants. Literature review and inputs from the clinicians was used to develop the questionnaire to ensure both validity and reliability of the study and the comparability of result across studies.

Confounders were controlled by restricting the study to only the HIV positive HAART naïve population enrolling at the clinic and the exclusion of those HIV patients with causes of ND identified by Daniel (1985). These changes included those attributable to other systemic diseases like kidney failure, diabetes or liver problems; changes caused by systemic drugs or ingestants like azidovudine (AZT) and emtrcitabine; changes attributable to local agents such as nail dyes and other topical agents; Changes attributable to some nail entities like those patients with separation of the nail plate from the nail bed. Other potential confounders that were measured included patient's age and gender. The sensitivity, specificity and positive predictive value of the test was calculated to determine the usefulness of ND.

3.7. Reliability

In order to ensure that someone else repeating the test using the same method should be able to obtain the same findings pilot testing of the questionnaires was undertaken. Clinicians enrolling patients were trained for proper identification and photographing of fingernails using

the nail color chart produced by Scarborough *et al.* (2006) as a guide. The clinicians were encouraged to sign their names on the questionnaire in order to ensure accurate work and make checking of records much easier. The patients were allowed to pass through the normal clinic procedures and were treated like any other patients for laboratory investigations, thereby ensuring that the laboratory scientists have no (prior) knowledge of the study. The identified and photographed ND from the clinicians was printed for other clinicians to identify the nail colors. Only the nail colors easily identified was used and others recorded as indeterminate.

Measurement errors due to individual biological variations was not a trait as the study was conducted with people of skin color similar to the Malawi study (Scaborough *et al.,* 2006).The Malawi study was carried out among patients of Fitzpatrick skin color of type IV. This is the color of skin shared among the black race (Derek, 1981 & Sachdeva, 2009), thereby ruling out errors resulting from individual biological variations.

3.8. Generalisability (External Validity)

Every individual race has a unique skin color type. For the black race, they share a common skin color type known as Fitzpatrick skin color type IV (Derek, 1981 & Sachdeva, 2009). All the adult ART naïve HIV infected patients attending APIN clinic belong to the black race, therefore, the study is only generalisable among the people of the black race.

3.9. Ethical Considerations

This study was approved and endorsed by the Higher Degree Committee of the University of the Western Cape in South Africa. Ethical clearance was then received from the Jos University Teaching Hospital/Human Research Ethics Committee (Appendix 4). Subsequently, final permission to conduct the study at the APIN clinic was received from the

APIN clinic research committee (Appendix 4). The nature of the study and participant information sheet (Appendix 1) was introduced to the prospective study participants by the respective interviewer. All patients consented to the research (see consent form, Appendix 2) by signing or thumb printing in line with the Helsinki declaration (WHO, 2001). Three patients were not up to 18 years. They accented to the study, while their parent consented for their participation. Patient's clinical management was not affected.

For patients having nail infections or other health conditions that was not clinically apparent to them appropriate referral for treatment was made. There were no physical or psychological harmful effects to participants that were expected from this study. The documents assured privacy and confidentiality of information collected from participants. The documents also assured the participants of their rights to withdraw from the study or refuse to participate in the study.

The researcher ensured that human subject were fully protected, responsibly conducted the research in line with good clinical practice following the guidelines provided by the Collaborative Institutional Training Initiative (CITI) , University of Miami, U.S.A. in collaboration with WHO (Appendix 6). Patient's data were collected and used anonymously; questionnaires were locked in a safe place accessible to the researcher only.

3.10. Data Analysis

3.10.1. Data Handling and Cleaning

Questionnaires were constantly checked during data collection to correct any query especially errors in data collection that arose. Questionnaires helped solve any query that arose during exploratory data analysis. Two separate views were created in Epi info version 3.5.1 (CDC,

2008) and the data from the questionnaires entered by two persons (the investigator and a statistician). The two entries were compared and any discrepancies such as double entries or strange values (outliers) were investigated. Using the Epi Info data analysis, all the variables were listed. Entries were compared again for any discrepancies. When implausible variables or values were obtained, the respective questionnaire was re-visited and data correction effected. Any value which could not be corrected by referring to the questionnaire was recorded as missing. Sixteen questionnaires were not entered for analysis as a result of unsigned consent forms or incompletely filled where vital information like age, sex were missing. This helped in reducing errors arising from measurement. This was followed by exploratory graphical data analysis and the exclusion of 31 indeterminate results including nails (Fig.2-4) before subjecting the data for real analysis. Data analysis was then carried out on a sample size of 394 respondents.

3.12.2. Variable Categorization

The categorization of variables was informed by the WHO updated guidelines. In terms of which all adolescents and adults including pregnant women with HIV infection and CD4 counts ≤ 350 cells/mm^3, should be started on ART regardless of whether they have clinical symptoms or not (WHO, 2010). Two cut-offs: CD4 count ≤200 and ≤350 cells/mm^3 was analyzed. This analysis employed both dichotomous variables and those that had more than two categories. The dichotomous variables were gender (male and female), ND (yes or no), ND with CD4 ≤ 200 cells/mm^3 (yes or no) and ND with CD4 ≤350 cells/mm^3 (yes or no). The results of the computation fell into six groups: positive change (ND) in nail color with CD4 count, positive change in nail color with CD4 count ≤200cells/mm^3 and positive change in nail color with CD4 count ≤350cells/mm^3, negative change (no ND) in nail color with CD4 count, negative change in

nail color with CD4 ≤200 cells/mm^3 and negative change in nail color with CD4 ≤350 cells/mm^3. Those who had a positive change were characterized as "yes" for the variable CD4 count, while those who had no color change were characterized as "no" for the variable.

Furthermore, to allow for group comparison of these data, age, highest level of education attained and occupations were all categorized. The age groups for the variables were 15-24, 25-34, 35-44, 45-54, 55-64, 65-74 and ≥75. The other variables groups were Highest level of education attained (no formal education, primary, secondary and post secondary education) and Occupation (Employed [farmer, civil servants, self employed], Unemployed [applicants i.e those looking for job] and others [students, house wife's, clergy, politician, politicians and business]). Finally, the nail color changes were categorized as normal nail color, distal banded or half and half nail, grey nails and indeterminate nails.

3.12.3. Descriptive, Analytical and Epidemiological Statistics (prevalence, sensitivity, specificity, positive predictive values and relative risk)

Descriptive analysis was conducted to structure the data, explore and describe the sample variable composition. Frequency tables for categorical variables like sex, ND (yes or no), ND with CD4 ≤ 200cells/mm^3 (yes or no) and ND with CD4 ≤350 cells/mm^3 (yes or no) and summary statistics for quantitative variables like age were made. Frequency tables of ND among various age groups and the types of nail colors were made. Also explored was the type of distribution of the different variables in the dataset. Mean and standard deviation of continuous variable was calculated. The CD4 was skewed hence the median and the inter quartile range were used to find the distribution while the mean and the standard were used for the age distribution since age had a

normally distribution. The association between ND and CD4 count was tested using the Chi-squared test when the expected cell values were less than 5.

The prevalence of ND and CD4 count of ≤ 200 and 350 cells/mm^3 in the population was calculated. This was followed by a screening test analysis to identify if ND could be a danger sign of immunosuppression in a HIV patient in WHO stage I & II. Four possible combinations were used. These combinations were: ND may either be present or absent, CD4 cell count less than 200cells/mm^3 or 350cells/mm^3 may either be positive or negative with ND. This was further categorized as:

- True positive (TP) : When ND is present and the test is positive (CD4 count ≤200 or 350 cells/mm^3)
- True negative (TN) : When ND is absent and the test is negative (CD4 count ≥200 or 350 cells/mm^3)
- False positive (FP) : When ND was absent and the test is positive (CD4 count ≤200 or 350 cells/mm^3)
- False negative (FN) : When ND was present and but the test result was negative (CD4 count ≥200 or 350 cells/mm^3)

These categories (TP, TN, FP and FN) were used for screening tests analysis to identify those that have ND and those without ND. The 2 x 2 table was used for comparison of test classification of those with ND (positive) and those without ND (negative). With 2 x 2 tables those who had ND (TP) and those without (TN) was identified and their sensitivity and specificity calculated. Those who were positive to ND had their PPV calculated to determine how believable the positive test was and NPV calculated to determine how believable the negative test was. Since 2 x 2 table looks at already existing disease, Prevalence was calculated

from the table. Looking at the overall 2 x 2 table, *Accuracy* was calculated to determine how correct the screening test results were. Accuracy looks at the overall test (TP, TN, FP and FN) rather than one column of the table. Accuracy is expressed mathematically as:

#

$$Accuracy = \frac{True\ Positive + True\ Negative}{Total\ Population}\ X\ 100$$

CHAPTER 4

RESULTS

4.1: Demographic characteristics of study participants

This study analysis consisted of 394. All study participants were 17 years of age and above. The mean (SD) age of the study participants was 33.1 (8.8) years. Most of the study participants fell into the age group 25-44 years while a minority was aged above 65 years. There was no difference between the age composition of the sample to that of the overall population of HIV patients who attend APIN clinic (P>0.05). The study sample demographic characteristic is presented in table 4.2 and 4.3, while table 4.4 shows the distribution of nail colors. Nail color distribution among participants with respect to level of education and occupation was explored (Table 4.5 and 4.6).

Table 4.2. Age distribution of study participants

Characteristics	**n (%)**	**P-value**
Sex		
Mean age (SD)	33.1 (8.8%)	0.7
Males	137 (34.8%)	
Mean age (SD) male	37 (9.4%)	0.9
Female	257 (65.2%)	
Mean age (SD) female	30.7 (7.1%)	0.1
Age group(yrs)	**Males(n=137)**	**Females(n=257)**
15-24*	6 (4.4%)	47 (18.3%)
25-34*	52 (38%)	133 (51.8%)
35-44*	45 (32.8%)	52 (20.2%)
45-54	24 (17.5%)	20 (7.8%)
55-64**	8 (5.8%)	4 (1.6%)
65-74**	2 (1.5%)	1 (0.4%)

*Age group 15-44 formed most of the sample with the females being the majority.
**55-74 were the least age group in the sample.

Table 4.3: Demographic characteristics of study participants compared with those of APIN Clinic

Highest level of education attained	**n (%)**	**APIN Clinic n (%)**	**P-value**
	394	19000	
No education	65 (16.5%)	3458 (18.2%)	.50
Primary education	67 (17%)	4009 (21.1%)	
Secondary education	146 (37.1%)	7980 (42%)	
Post secondary education	116 (29.4%)	3553 (18.7%)	
Occupation			
Employed (Farmer civil servants)	168 (42.6%)	8930 (47%)	.50
Unemployed (applicant)	24 (6.1%)	1406 (7.4%)	
Others (artisans, business, students e.t.c)	203 (51.2%)	8664 (45.6%)	
Year of HIV diagnosis			
2005	3 (0.8)		
2006	9 (2.3)		
2007	29 (7.4)		
2008	123(31.2)		
2009	176 (44.7)		
2010	54 (13.7)		

Table 4.4: Distribution of nail colors

Characteristics	**n (%)**	**P-value**
Without ND	245 (62.2%)	
With ND	149 (37.8%)	0.0001

Table 4.5. Level of education and distribution of nail colors

Nail color	**None**	**Primary**	**Secondary**	**Post secondary**
Without ND	52 (80%)	47 (70.1%)	77 (52.7%)	69 (59.5%)
Distal banded	7 (10.8%)	8 (11.9%)	41 (28.1%)	25 (21.6%)
Grey nails	6 (9.2%)	12 (17.9%)	28 (19.2%)	22 (19%)

Table 4.6. Occupation and distribution of nail colors

Nail colors	Farmers	Civil servants	Students	Applicants	Business	Others
Without nail discoloration	46(%)	47(46.6%)	29(61.7%)	16(66.7%)	23(71.9%)	84(68.3%)
Distal banded	15(22.4%)	31(30.7%)	11(23.4%)	4(16.7%)	4(12.5%)	16(13%)
Grey	6(9.0%)	23(22.8%)	7(14.9%)	4(16.7%)	5(15.6%)	23(18.7%)

4.2. Nail Characteristics

The study participants nail colors were classified as those with normal nail colors, those with distal banded nails (popularly called half and half nail in the clinic) and grey nails. Some participants have both grey and distal banded nails occurring together but the most prominent nail color identified was chosen (Fig.9). Clinicians could not agree on what constituted DCO thus making it difficult to identify and subsequently excluded from the study. Those with normal nail colors were more in the study. Distal banded and grey nails affected all the fingernails and distal banded nails was the commonest of the nail discolorations and the easiest to identify. It can easily be identified in a bright (indoor) light. Figures 5 to 9 shows the study participants nail distribution, the percentages of nail distribution and types of nail colors.

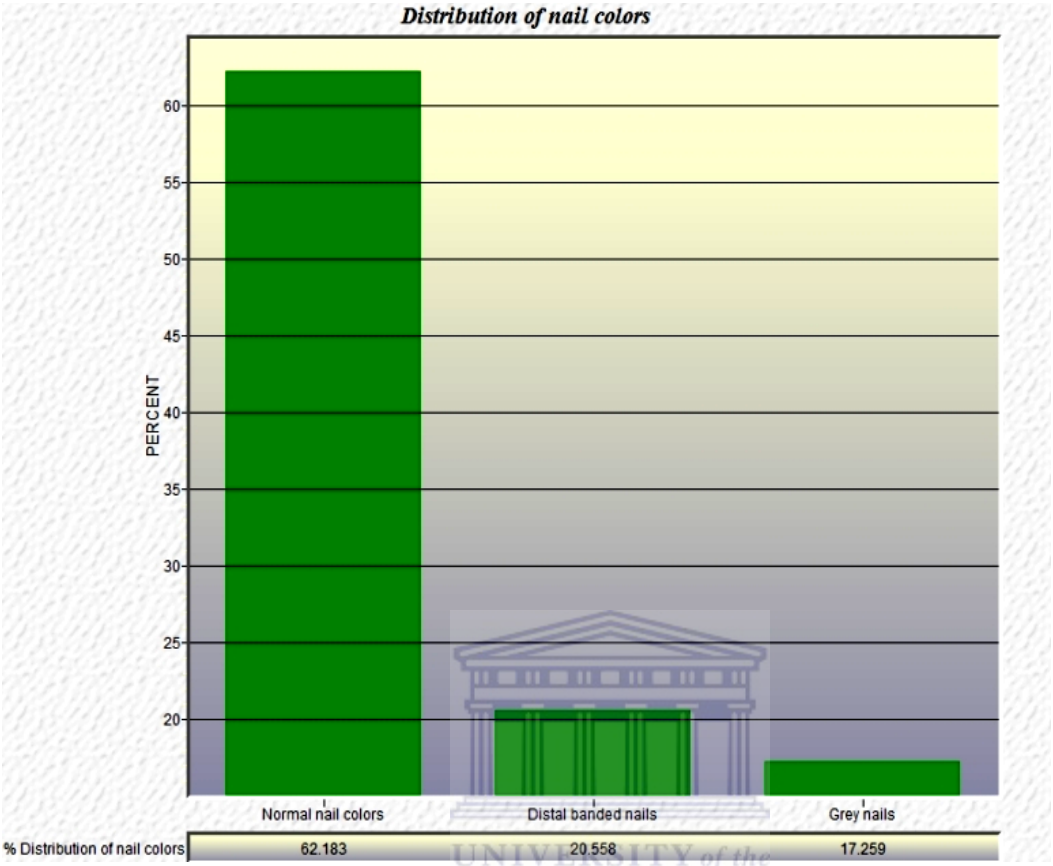

Figure 5: Distribution of nail colors giving the prevalence of distal banded and grey nails

Figure 6: Normal nail colors

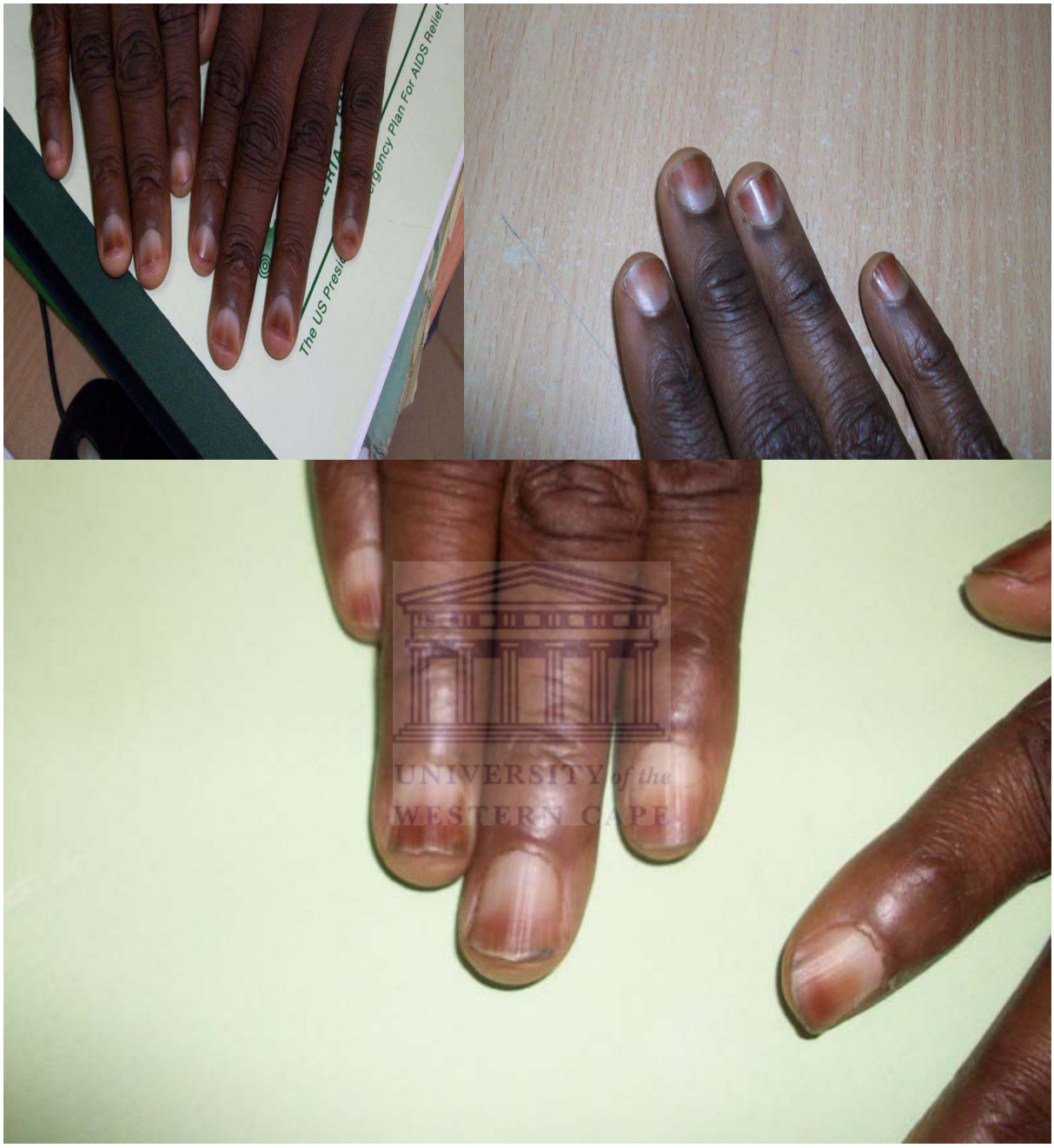

Figure 7: Distal banded or half and half nail colors

Figure 8: Grey nails

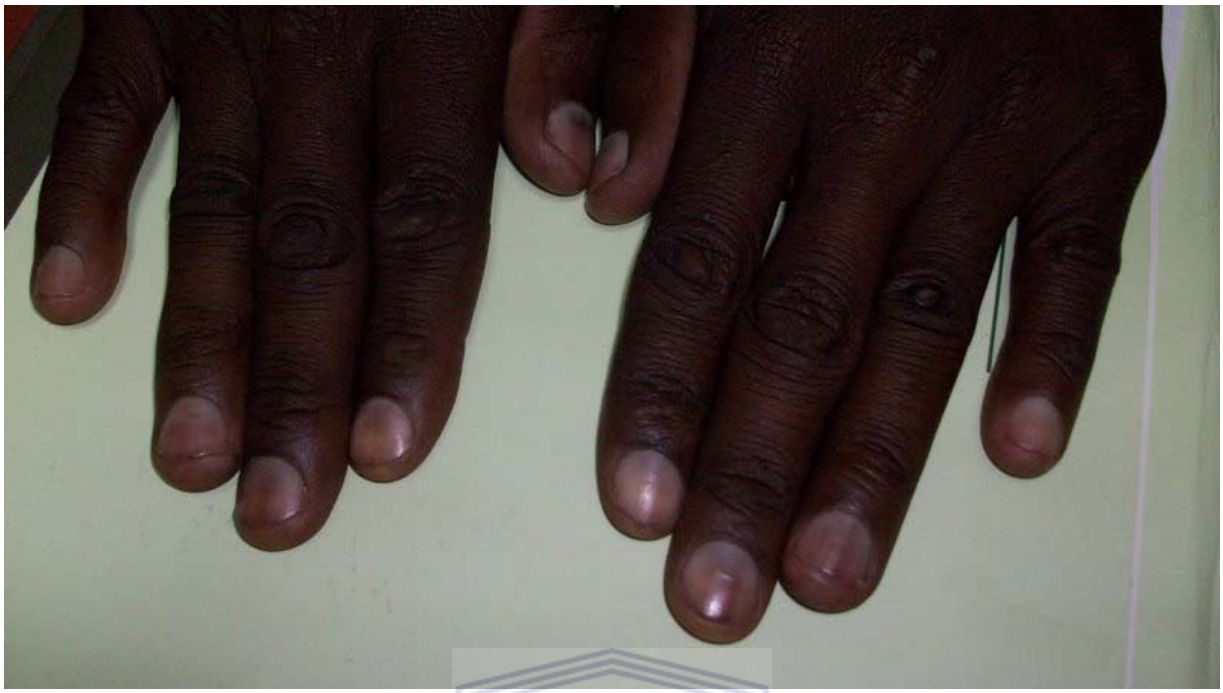

Figure 9. Grey nails with distal bands

4.3. Immune status of subjects

The relationship between nail colors and CD4 count was also explored. These relationships was analysed separately among those with a CD4 cell count of less than 200cells/mm^3 and those with a CD4 cell count of less than 350cells/mm^3. There was a relationship between the CD4 count and the nail colors ($P<0.0001$). Table 4.7 shows the immune status of subjects. Immune status of subject by gender and age group is shown in table 4.8 and 4.9.

4.4: Relationship between nail colors and immune status of subjects

Participants within the age groups 15-44 years presented more to the clinic with a CD4 count of ≤200 ($p<0.0001$) and 350 cells/mm^3 ($p<0.0003$) with those >45 having the least presentation (Table 4.9).

Two hundred and thirty two (232) (58.8%) had their CD4 count less than 200cells/mm^3.Those with distal banded nails had the highest number of ND seen. Grey nails were the least recorded nail discoloration seen when compared with the participants CD4 count. Table 4.10-4.12 shows the relationship between these nail colors and the participants immune status.

Table 4.7: Immune status of subjects

Characteristics	N (%)	P-value	R.R (CI)
≤200cells/mm^3	232 (58.9)	<0.0001	2.6 (1.8-3.6)
≥200cells/mm^3	162 (41.1)		
≤350cells/mm^3	305 (77.4)	0.002	1.9 (1.3-3.0)
≥350cells/mm^3	89 (394)		
Median CD4(IQR)	175 (89-317)		

Table 4.8: Immune status of subjects by gender

Immune status	Male (n=137)	Female (n=257)
≤200cells/mm^3	90 (65.7%)	142 (55.3%)
≥200cells/mm^3	47 (34.3%)	115 (44.7%)
≤350cells/mm^3	113 (82.5%)	192 (74.7%)
≥350cells/mm^3	24 (17.5%)	65 (25.3%)

Table 4.9: Immune status of subjects by age group

Age group	**≤200cells/mm^3**	**P=value**	**≤350cells/mm^3**	**P=value**
15-44	194 (57%)	0.0001	307 (77.9%)	0.0003
>45	38 (64.4%)	0.3	48 (15.6%)	0.2
Age group	**≤200cells/mm^3**	**≥200cells/mm^3**	**≤350cells/mm^3**	**≥350cells/mm^3**
15-24	21 (39%)	32 (60.4%)	34 (64.2%)	19 (35.8%)
25-34	113 (61%)	72 (38.9%)	147 (79.5%)	38 (20.5%)
35-44	60 (61.9%)	37 (38.1%)	76 (78.4%)	21 (21.6%)
45-54	29 (65.9%)	15 (34.1%)	36 (81.8%)	8 (18.2%)
55-64	8 (66.7%)	4 (33.3%)	10 (83.3%)	2 (16.7%)
65-74	1 (33.3%)	2 (66.7%)	2 (66.7%)	1 (33.3%)

Table 4.10: Relationship between nail colors and gender

Sex	**Male (n=137)**	**Female (n=257)**
Normal nail colors	75 (54.7%)	170 (66.1%)
Distal banded nails	26 (19%)	55 (21.4%)
Grey nails	36 (26.3%)	32 (26.3%)

Table 4.11: Nail color by immune status

Participants	**Participants level of CD4 counts (Immune status)**		
	≤200cells/mm^3	**201-350cells/mm^3**	**≥350cells/mm^3**
No. of participants	232 (58.8%)	89 (22.6%)	73 (18.5%)
Nail discoloration	117 (50.4%)	13 (17.8%)	19 (21.3%)
Without nail discoloration	115 (49.9%)	60 (82.2%)	70 (78.7%)
Normal nail colors	115 (46.9%)	60 (24.5%)	70 (28.6%)
Distal banded nails	62 (76.5%)	4 (4.9%)	15 (18.5%)
Grey nails	55 (80.9%)	9 (13.2%)	4 (5.9%)

Table 4.12: Nail colors by age group

	Participants nail distributions		
Age group	**Normal nail**	**Distal banded**	**Grey nails**
15-24	37 (15.1%)	10 (12.3%)	6 (8.8%)
25-34	109 (44.5%)	42 (51.9%)	34 (50%)
35-44	59 (24.1%)	18 (22.2%)	20 (29.4%)
45-54	29 (11.8%)	9 (11.1%)	6 (8.8%)
55-64	9 (3.7%)	1 (1.2%)	2 (2.9%)
65-74	2 (0.8%)	1 (1.2%)	0 (0.0%)

4.5. Significant testing and screening tool evaluation

The sample size of 394 was further subjected to a significant testing and to evaluate the strength of association between ND and CD4 count levels. Using a 2x2 table shows that there was a significant association (p>0.0001). The strength of this association was evaluated using the relative risk and the confidence intervals. Significant testing of participants with CD4 cell counts of ≤200cells/mm^3 and ≤350cells/mm^3 were analysed separately (Table 4.13 and 4.14). CD4 ≤350cells/mm^3 was added because of the new ART guidelines released by WHO which Nigeria will soon adopt.

4.6. Strength of association between CD4 ≤200c/mm^3 and CD4 ≤350 cmm^3

Nail discoloration was found to be associated with both CD4 counts of ≤200 and 350 cells/mm^3 (p<0.00001 & 0.002). But the strength of association increases with CD4 counts of ≤ 200cells/mm^3 (R.R; 2.3(1.8-3.6) as shown by the increasing number of participants 117(50.4%) with ND with CD4≤200cells/mm^3 (Table 4.13). There is a better specificity and positive predictive values with a CD4 cell count of less than 200cells/mm^3. The positive predictive values, specificity and strength of association between ND and CD4 count decreases with CD4 cell count greater than 200cells/mm^3 as seen in this study. Looking at the overall test in the 2 x 2 table, accuracy (63%) was better among those participants with CD4 count ≤200cells/mm^3, than those participants who had their CD4 count ≤ 350cells/mm^3 with an accuracy result of 51%.Out of the total 130 (68.2%) with ND, 117(50.4%) had CD4 ≤200cells/mm^3 with 13(17.8%) participants had their CD4 count fell between 201 to 350c/mm^3. Those with CD4 count ≤ 350cell/mm^3 had a poor specificity and low PPV when compared with those with ≤200cell/mm^3. The sensitivity is higher among those with a CD4 count ≤350cells/mm^3 (87%) (Table 4.14),

which could have been due to more number of participants 13 (17.8%) for those populations with CD4 ≤350cells/mm^3. Participants with CD4 count ≤200cells/mm^3 and ND has a better, strength of association (p<00001), specificity (55%) and PPV (50%) than participants with CD4 ≤350cells/mm^3.While the NPV for participants with ≤200 and 350 cells/mm^3 were not really different (80% and 79%).

Since CD4 count ≤200 cells/mm^3 has a better strength of association, with good sensitivity and specificity, good PPV and NPV and a better accuracy, it will be used for the discussion and conclusion part of the data analysis.

Table 4.13: Significance testing and screening test evaluation of association between ND and CD4 count ≤200 cells/mm^3

	Positive (+) **CD4 ≤200cells/mm^3**	**Negative (-)** **CD4 ≥200cells/mm^3**	
Positive (+)	117	115	232
Negative (-)	32	130	162
Total	149	245	394

- Sensitivity = 78%
- Specificity = 55%
- Positive predictive value = 50%
- Negative predictive value = 80%
- Relative Risk (Confidence Interval, CI)= 2.3 (1.8-3.6)
- Prevalence = 38%
- Accuracy = 63%
- P=value= 0.00001

Table 4.14: Significance testing and screening test evaluation of association between nail discoloration and CD4 count ≤350 cells/mm^3

	Positive (+) **CD4 ≤350 cells/mm^3**	**Negative (-)** **CD4 ≥350 cells/mm^3**	
Positive test n(+)	130	175	305
Negative test (-)	19	70	89
Total	149	245	394

- Sensitivity= 87%
- Specificity= 29%
- Positive predictive value= 43%
- Negative predictive value= 80%
- Relative Risk (Confidence Interval, CI) = 1.99(1.3-3.0)
- Prevalence = 38%
- Accuracy = 51%
- P-value =0.003

CHAPTER 5

DISCUSSION AND STUDY LIMITATIONS

5.1. Discussion

This study has provided insight on the association of nail discoloration in HIV patients with CD4 count of ≤200 cells/mm^3. All study participants were 17 years of age and above. The 394 study participants had their nails compared with their levels of CD4 count for association. The results has shown that low CD4 count of ≤200 cells/mm^3 is a risk factor for ND and has a significant association with distal banded and grey nails which could enhance the management of patients found to be HIV positive ($p<0.0001$; R.R:2.3[1.8-3.6]). The prevalence of ND is 38% and an accuracy of 63%. This deduction was made with a study sample of 394 participants with most of them within the age range of 15-44 years which is the age group commonly affected by HIV/AIDS (FMOH, 2005) in Nigeria. This age group of 15-44, had 194 (57.9%) presented with nail colors with a CD4 count of ≤ 200cells/mm^3 which is significant ($p<0.0001$). Females (n=257; 65.2%) made up of the majority of the study sample reflecting the unequal sex composition of the adult ART clinic as against their male counterpart who were made up of 137 (34.8%) of the study sample. This is in conformity with the sex distribution of patients at the APIN clinic (APIN clinic record) with a male to female ratio of 1:2.

The highest level of education attained and occupational distribution of the study was not different from that of APIN clinic ($p>0.5$). Comparing nail distribution among participants highest level of education and occupation shows a near even distribution of nail discolorations in all the participants irrespective of their level of education and occupations. These near even distributions now serve as a pointer to a more systemic cause with immunosuppression being the

most likely cause. This was so, because association was found to exist between the CD4 count (participants immunity) and the nail colors ($p<0.0001$). Relative risk was used to measure the strength of these relationship which indicated that the CD4 count was a risk factor for nail color change with a R.R of 2.6 (confidence interval: 1.8-3.6).

Previous reports have shown that nail discoloration associated with those who are HIV positive were regularly found in subjects with immunosuppression and CD4 count ≤200cells/mm^3 (Cribier *et al.,* 1998; Scaborough *et al*., 2006 & Namakoola *et al.*, 2010). An overall prevalence of 38% in this study is higher than the 19% reported by Levay, Botes & Malela, 2005 in patients attending immunology clinic at Pretoria, South Africa. It is still not clear whether this difference could be attributed to racial or environmental factors, especially as my study was carried out among patients of Fitzpatrick skin color type IV to which the black race belong (Derek, 1981 & Sachdeva, 2009).This may not necessary be the same for the Pretoria study. This prevalence would have been higher if there was uniform nail color identification among the clinicians. In spite of the color chart produced by Scaborough *et al*., (2006) which served as a guide, differences in color perception still occurred. Clinicians could not agree on what constitute DCO during the study. This area of color perception requires more skills among clinicians in order to identify ND as a result of immunosuppression especially with grey nails.

A review of studies shows that distal banded nails/grey nail was strongly associated with a CD4 count of ≤200cells/mm^3 (chi-squared=0.0001) (Scaborough *et al*., 2006 & Namakoola *et al.*, 2010). With a sensitivity of 78%, a specificity of 55%, a PPV of 50% and a NPV of 80% when compared with other studies shows that close similarities exists between sensitivity and specificity with Scaborough *et al*., 2006 study but differed in PPV. Scaborough *et al*. (2006) & Namakoola *et al.*, (2010) studies had a higher PPV's of 81% and 77% compared to 50%

recorded by my study. This research finding had a close similarity in NPV (80%) with Namakoola *et al.*, (2010) record of 77% but differed in sensitivity and specificity. Namakoola *et al.*, (2010) had a lower sensitivity of 66% and specificity of 50%.

In spite of the low sensitivity reported by Scaborough *et al*. (2006), the authors noted that most clinical markers of HIV progression had low sensitivity and that 75% of HIV infected individuals with grey/distal banded nails were denied ART using current clinical criteria. They therefore, recommended the use of grey/distal banded nails in resource limited setting to help patients to benefit from ART. This recommendation was contrasted by Namakoola *et al.*, 2010, who argued that sensitivity results were rather too low for this method to be recommended as a tool to guide for ART initiation. This was so because a large individual group eligible for ART will be missed.

The current study, calculated values specificity of 55%, sensitivity of 78% and a PPV of 50% tend to agree with Scaborough *et al*. (2006). One hundred and seventeen (or 50.4%) participants with distal banded nails and grey nails had a low CD4 count ≤200cells/mm^3, so were eligible for ART. This eligibility suggests that distal banded and grey nails could assist in identifying those who may be in need of ART. Differences between sensitivity results obtained in this study and that of Scaborough *et al*., (2006) and Namakoola *et al.*, (2010) raise an unanswered question around causation and association in respect of ND and CD4 count. If CD4 count ≤200 cells/mm^3 has an association with ND, is it likely that CD4 ≤200 cells/mm^3 can cause ND? The answer to this question can help to resolve these differences encountered by Scaborough *et al*. (2006) and Namakoola *et al.*, 2010 studies. Prospective epidemiological studies will be required to clarify this question.

5.2. Study Limitations

1. The cross-sectional study design was not able to establish if low CD4 count of ≤200cells/mm^3 was a cause of ND.

2. The consultant dermatologist left the APIN programme at the middle of data collection, leaving clinicians with difficulty in arriving at a consensus about ND and what constituted DCO and its identification. These led to fewer questionnaires being analyzed as most were invalid.

3. Misclassification bias especially for grey nails which was sometimes regarded to as blue nails leading to exclusion.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

6.1. Conclusions

This mini-thesis reports on a survey on ND and its association with CD4 count among untreated HIV patients at APIN centre, JUTH. The mini-thesis was not only concerned with estimating the prevalence of ND in a sample of untreated patients and determining the association of ND and immunosuppression among the patients, but also aimed to characterise the types of ND seen, and further determine the sensitivity, specificity and predictive values to see if it could be effective in initiating ART in group of persons likely to benefit from ART.

This research had shown that ND had a prevalence of 38% among treatment naïve patients attending APIN Centre Clinic and that an association exited between CD4 count of ≤200cells/mm^3, with an accuracy of 63%. The study had further shown that CD4 count of ≤ 200cells/mm^3 was a risk factor for developing ND. Distal banded and grey nails were the commonest ND found. With a very strong significant association (p=0.0001) and a sensitivity of 78%, ND can be a useful clinical indicator of early immune dysfunction mediated by HIV among patients in WHO stage I or II. The specificity and sensitivity of ND compared favourably with other WHO stage III diagnosis (Terk's *et al.,* 2005 & Scarborough *et al*., 2006). Sensitivity, PPV and Specificity though not too sufficiently high for a sound screening test was better than having a random guess. This research was meant to complement the CD4 count used as a diagnostic criterion for the commencement of ARV's.

Out of the 394 (100%) of the HIV infected individuals, 232 (58.8%) had CD4 ≤200 cells/mm^3 and 117(50.4%) had ND and were, qualified for ARV using the current clinical criteria. ND could either be a clinical sign or a symptom in HIV patients with a CD4 of ≤ 200cell/mm^3 as seen in this study. In view of this significant association between ND and low CD4 count; the following recommendations could be useful:

6.2. Recommendations

6.2.1. Recommendation 1

That the screening for ND should complement CD4 count as an additional staging sign to help identify patients likely to benefit from ART especially in resource limited settings and ND can be used as a screening tool to evaluate the immune status of HIV infected population in HIV care and treatment programmes considering the prevalence level of 30%.

6.2.2. Recommendation 2

That all patients with ND should be placed on co-trimoxaxole prophylaxis in line with WHO /national guideline recommendation on the use of co-trimoxaxole for all HIV positive patients with a CD4 cell count of ≤350cells/mm^3 (PEPFAR, 2009). This is so because out of the 149 participants that presented with ND, 130 (87.2%) presented with ND and CD4 count of ≤350cells/mm^3 ($p<0.0003$) with the remaining 19 (12.8%) participants with ND having CD4 ≥350cells/mm^3.

6.2.3. Recommendation 3

There should be a massive community awareness campaign to educate the public on the need to go for a VHCT whenever they notice any recent change in nail colors as it could be a sign of HIV infection with severe immunosuppression.

6.2.4. Recommendation 4

Clinicians and other health care workers should be trained on how to identify and to watch out for nail color changes in a HIV positive patients so that they can benefit from early ART in view of the high prevalence. Those working in health care centres should be encouraged to always examine all patients' nails in order to identify those who may not be aware of their status but may have asymptomatic HIV with severe immunosuppression. This is important especially at the Primary Health Care level.

6.2.5. Recommendation 5

Further research is required to see if distal banded, grey nails can be a more diagnostic tool other than a screening tool for it to have a maximum utilisation in resource-poor settings without a CD4 cell count testing machine.

6.2.6. Recommendation 6

Since association exists between CD4 count of $\leq$ 200cells/mm^3 and ND, further studies is required to determine if CD4 count of $\leq$200cell/mm^3 is causation for ND.

REFERENCES

Abdulsalam, N. & Tekena, O. (2006). Ch 2-The Epidemiology of HIV/AIDS in Nigeria. In: Olusoji, A., Phyllis, K., Oluwole, O. & Idoko, J. (eds).*AIDS in Nigeria: A Nation on the Threshold.* Havard: Havard Center for Population and Development Studies, Boston: 17-19.

Aftergut, K. (1999).Update on Cutaneous Manifestations of HIV Infection Clinical and Pathologic Features. *Journal Dermatology* 17(3): 445-471).

Abimiku, A. (2009). Building Laboratory Infrastructure to Support Scale-up of HIV/AIDS Treatment, Care & Prevention: In-Country Experience. *American Journal of Clinical Pathology* 131(6): 875-86.

Asokan, P., Criton, S. & Mohan, K. (1995). Dermatological Manifestation of HIV Infected/AIDS Patientsin a Refferal Hospital of Central Kerela. *Indian Journal of Dermatology* 61(2): 89-90.

Beaglehole, R. Bonita, R. & Kjellstrom, T. (2006). Ch6-Epidemiology and Prevention of Chronic Non-Communicable Diseases: *Basic Epidemiology*. Geneva, WHO Press: 117-130.

CDC (Centers for Disease Control and Prevention). Epi Info Version 3.5.1. [Online]. Available: http://www.cdc.gov/epinfo/.[Downloaded:11/11/2009 12:30 P:M.]

Chandrasekar,P.(1989). Nail Discoloration and HIV Infection Related. *Pub Med 86(4):506-507*

Chernosky, M. & Finley, V.(1985). Yellow Nail Syndrome in Patients with Acquired Immunodeficiency Disease. *Journal American Academy of Dermatology 13(15 pt 1):731-736.*

Choi, C. (2002). *Anatomy of The Skin.*[Online]. Available: http// wounds/ com/ News/ Main Story. cfm. [Downloaded: 11/06/09 01:21 P:M].

Cribier, B., Leiva, M. ,Rey, D., Partisani, M., Fabian, V. , Lang, J. & Grosshans, E.(1998). Nail Changes in Patients Infected with Human Immunodeficiency Virus. *Archives of Dermatology* 134:1216-1220.

Daniel, C., Norton, L.& Scher, R. (1992).The Spectrum of Nail Diseases in Patient with HIV infection. *Journal American Academic Dermatology* 27: 93-97.

Daniel, C. (1985). Nail Pigmentation Abnormalities. *Clinical Dermatology* 3(3): 431 – 443.

Dawson, B. & Trapp, R. (1994). *Basic and Clinical Biostatistics*. New York: Lange Medical Books/McGrew-Hill.

Derek, C. (1981). Natural and Artificial Photoprotection. *Journal of Investigative Dermatology 77: 154-157.*

Dean, A., Sullivan, K. & Soe, M. (2009).*Open Source Epidemiological Statistics for Public Health, Version 2.2.1.* [Online]. Available: www.OpenEpi.com.[Downloaded: 02:02:09 12:44 P:M].

DermWeb. (2009). *Hair, Nails and Mucous Membrane.* [Online]. Available: http:// www. dermweb. Com /hairnailsmucousmembranes /nails.htm.[Downloaded: 26/08/2009 08:15 A:M].

Dover, J. & Johnson, R.(1992).Cutanous Manifestation of Human Immunodeficiency Virus Infection. *Archives of Dermatol*ogy 127: 1383-1391.

Erdal, E., Zalewska, A., Schwartz, R. & Hamadeh, R. (Updated, 2007). *Cutanous Manifestation of HIV Diseases*. [Online]. Available: http://emedicine. medscape.com /article/ 1333746-erview. [Downloaded: 19/01/09 10:10 A:M].

Fathalla, M. (2004). *A Practical Guide for Health Researchers*. WHO eastern Mediterranean Cairo. WHO.

FMOH (Federal Ministry of Health). (2006). *2006-2010 National Strategic Frameworks for Implementing TB/HIV Collaborative Activities in Nigeria*. Abuja: Federal Ministry of Health.

FMOH. (2005). *Guidelines for the Use of Antiretroviral Drugs in Nigeria*. Abuja: Federal Ministry of Health.

Glaser, D. & Remlinger, M.(1996).Blue Nails and Acquired Immunodeficiency Syndrome: Not always Associated with Azidovudine use. *Journal American Academy of Dermatology* 57(4): 243-244.

Gregorion, S., Angyriou, G., Larios,G. & Rigopolos, D. (2008). Nail Disorders and Systemic Disease: What the Nail tells US. *The journal of Family Practice* 57(8): 509-514.

Herzberg, A. (2004).Nail Manifestations of Systemic Diseases. *Journals of Clinics of Podiatric Medicine and Surgery of North America* 21(4): 631-640.

Katzenellenbog, M., Joubert. G, & Karim, S. (1997). Ch8- Sampling .In Epidemiology: *A Manual for South African*. Cape Town: Oxford University Press: 74-82.

Leppard, B. (1999). Blue nails are sign of HIV infection. *International Journal of STD ,10: 497-482*.

Levay, P., Botes, E. & Malela, E. (2005). Dyschromonychia: Clinical Significance in a South African Population. *South African Family Practice Journal* 47 (8): 54-59.

Lynen, L. (2008). *Natural Evolution of HIV*. [Online]. Available: http://telemedicine.itb.be/. [Downloaded: 25/04/09 12:30 A:M].

Martis, W., Triana, A., Shapiro, R., Eldred, L., Polk, B. & Hood ,A.(1987). Dermatologic Findings Associated with HIV Infection. *Journal of the American Academy of Dermatology* 17: 746-751.

NACA (National Agency for the Control of AIDS). (2010). *National HIV/AIDS Statistics 2009)*. [online]. Available: http://www.naca.gov.ng/. [Downloaded: 08/12/2010 06:44 P:M].

Nagalingeswaran, K., Saniti, S., Purnim, M., Balakrishnan, R., Panchatcharam, T. & Patrick, Y. (2000). Dermatological Manifestations among HIV Patients in South India. *International journal of dermatology* 39: 192-195.

Namakoola, I., Wakeham, K., Parkes-Ratanshi, R., Levin, J., Mugagga, T., Seymour, C., Kissa, J., Kamali, A. & Lalloo, D. (2010). Use of Nail and Oral Pigmentation to Determine ART Eligibility among HIV Infected Ugandan Adults. *Tropical Medicine International Health 15(2): 259-262.*

National Population Commission. (Preliminary census result, 2006). *Vital Registration Department*. [online]. Available: http://www.idr.ca/en/ev/101616_-201_do_topic.html. [Downloaded: 13/03/08 12:45 P:M].

Olaleye, O., Tekena, H. & Odaibo, G. (2006).Ch3-The Virology and Dynamics of the Epidemic. In Olusoji, A., Phyllis, K., Oluwole, O. & Idoko, J. (eds).*AIDS in Nigeria: A Nation on the Threshold.Havard:* Havard Center for Population and Development studies, Boston: 45-47.

Onwujekwu, D. (2007). Positive Moments [Treatment Education]. [online], Available: http://www.pata.nigeria.com/.[Downloaded: 08/12/2010 07:02 P:M]

Pitcher, C., Honing, S., Fingerhut, A., Bowers, K. & Marsh, M. (1999). Cluster of Differentiation Antigen 4 (CD4) Endocytosis and Adaptor Complex Binding Require Activation of the CD4 Endocytosis Signal by Serine Phosphorylation. *Molecular Biology of the Cell 10: 677-691*.

Panwalker, P. (1987). Nail Pigmentation in the Acquired Immunodeficiency Syndrome. *Journal of American Internal Medicine 107(6): 943-4.*

Pros, N., Asson, K. & Scher, R. (2007). Disorders of the Nails and Hair association with Human Immunodeficiency Virus Infection*. International Journal of Dermatology* 31:453-457.

President's Emergency Plan for AIDS Relief (PEPFAR). (2009). *Adult Antiretroviral Treatment Protocol.* Harvard School of Public Health, Boston: 42-45.

Rehmus, W. (2007). *Nail Disorders: Deformities and Discoloration.* [Online]. Available: http://www.merk.com/mmhe/sec18/ch216666.html. [Downloaded: 18/01/09 05:21 P:M].

Richard, L., Donald, B. & Richard, B. (2008). *DeGowin's Diagnostic Examination* .[Online]. Available:http://books.google.com.ng/books?id. [Downloaded: 26/08/09 09:49 A:M].

Reynaud-Mendel B., Janier, M., Gerbaka, J., Harkim, C., Rabian, C.,Chasteng, C. & Morel, P. (1996). Dermatologic findings in HIV-1 Infection Patients: A Prospective Study with Emphasis on CD4 Cells. *International Journal of Dermatol*ogy 192(4): 325-328.

Rizos, E., Drosos, A. & Ioannidis, J. (2003). *Nail Pigmentation and Fatigue in a 39 –year-old Woman*.[Online]. Available: http://www.rheumatology.gv/reprints_drosos. [Downloaded: 19/01/09 18:01 P:M].

Rice, P. & Ezzy D. (1999). Sampling Strategies for Qualitative Research In: *Qualitative Research Methods -A health focus*. Sidney: Oxford University Press: 40-50.

Sachdeva, S. (2009). Fitzpatrick Skin Typing: Applications in Dermatology. *Indian Journal of Dermatology75:1*

Scaborough, M., Gordon, S., French,N., Phiri, C., Musaya, J. & Zijlstra, E. (2006). Grey Nails Predict Low CD4 Cell Count among untreated patients with HIV Infection in Malawi. *AIDS journal* 20(10): 1415-1417.

See, J. & Wong, D. (2007).HIV Infected Patients: Correlation of Cutanous Disease with Degree of Immunosuppression. *Australian Journal of Dermatology* 33(3): 151-153.

SkinInc. (2007). *SkinType*. [Online]. Available: http://www.skininc.com/skinscience/physiology. [Downloaded: 11/06/2009 03:13 P:M]

Smith, K., Skelton, H., Yeager, J., Leusky, R., McCarthy, W., Baxter, D. & Wagner, K.(1994). Cutaneous findings in HIV-1 Positive Patients: A 42-months Prospective Study. *Journal of the American Academy of Dermatology* 31(1): 746-754.

Sindrup, J., Lisby, G., Weismann, K. & Wantzin, G. (2007). Nail Changes Association with HIV Infection. *International Journal of Dermatology* 26(5): 267-272.

Stephen, A. (2008). Epidemiological Statistics, Sensitivity and Specificity and Kappa Statistics: In: *Research Method and Statistics*. Jos: JUTH Research & Continuing Medical Education Unit: 13-19.

Tse, I. (2007). *Dermatologic Manifestation in HIV Diseases.* [Online]. Available: http://www.info.gov.hk/aids/pdf/g.190htm/iv_index.htm. [Downloaded:30/03/09 09:35 A:M].

Terk, R., Ascurra, O., Gomani, P., Mauzi, M., Pasulani, O., Kusamale, J., Salaniponi, M., Humblet, P., Nunn, P., Scano, F., Harris, D. & Zachariah. (2005).WHO Clinical Staging of HIV Infection and Diseases, Tuberculosis and Eligibility for Antiretroviral Treatment: Relationship to CD4 Lymphocyte Counts. *International Journal of Tuberculosis of Lung Disease 9(3): 256-262*.

UNAIDS/WHO. (2008*). HIV/AIDS AND STATISTICS for SUBSAHARAN AFRICA*. Geneva: UNAIDS/WHO.

UNAIDS/WHO. (2007*). AIDS Epidemic Update*. Geneva: UNAIDS/WHO.

UNICEF/Nigeria. (2007). *Information Sheet: HIV/AIDS*. [Online], Available: http:/ /unicef.org/wcaro_nigeria_factsheet_HIV-AIDS.pdf. [Downloaded:11/01/09 03:17 P:M].

USAID (2008). Nigeria HIV/AIDS Service Provision Assessment 2008. Washington, D.C: USAID.

WHO. (2001). *Health Research Methodology: A Guide for Training in Research Methods*. WHO. Geneva.

WHO. (2010).*2009 WHO ART Guidelines for Adults and Adolescents.* [Online]. Available: http: //www.who.int/ihv/topics/treatment.[Downloaded: 09/06/2010 09:27 A:M].

Woo, K. & Sibbard, G. (2007). Common Nail Disorders and Fungal Infections. *The Journal for Prevention and Healing* 20(6): 346-357.

APPENDIX 1: Participant information sheet

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PARTICIPANT INFORMATION SHEET

I am Ekeh Peter Nnamdi, a student studying for the Master's in Public Health at the University of the Western Cape, South Africa. I am gathering information from adult above the age 15 years. I am trying to find out the use of Nail Discolouration as a Screening Tool for Predicting low CD4 count in a Resource Limited Setting.The study will be used for obtaining a degree. I would like to ask you some questions which will take about 10-20 minutes of your time. You may choose not to participate in this study and your refusal will not affect you in any way. Whatever information you give me will not affect the care you receive from the clinic, and will not be given to anyone else except for improving the ART programme. The information collected will help us improve the utilization of ART services in this district.

Do I have your permission to continue with my questions? □ 1=yes 2=no

Signature:_____ Date:_____

Researcher's name: EKEH PETER NNAMDI

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Should you have any questions regarding this study or wish to report any problems you have experienced related to the study, please contact the study coordinator:

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APPENDIX 2: Consent form

RECORD OF AN INFORMED CONSENT TO CONDUCT AN INTERVIEW

Date: 15/05/09

Interviewer's name: Ekeh Peter Nnamdi

Tel: +2348027056425 or +2347035395941

UWC Student no: 2831634

E-mail: petekiae@yahoo.com

Institution: University of the Western Cape

Interviewees' pseudonym:

Place at which the interview was conducted: Harvard PEPFAR APIN HIV/AIDS Clinic (APIN Centre), Jos University Teaching Hospital, Jos, Nigeria.

Thank you for agreeing to allow me interview you. What follows is an explanation of the purpose and process of this interview. You are advised to give your consent for me to conduct an in-depth interview with you and to use this data for an assignment for my studies at the School of Public Health, UWC.

1. Information about the interviewer

I am Ekeh Peter, a student at the SOPH, University of the Western Cape. As part of my Masters in Public, I am required to carry out a research. I will be focusing on finding out the use of Nail Discolouration as a Screening Tool for Predicting low CD4 count in a Resource Limited Setting. I am accountable to Dr Ehimario Igumbor who is contactable at 021 959 3520/Cell: 082 920 0613 or c/o SOPH Fax: 021 959 2872 or by e-mail at eigumbor@uwc.ac.za

Here is some information to explain the purpose and usage of my interview.

2. The purpose and content of my interview [The purpose of my interview is to fulfil the part of my Masters in Public Health. The content will be questions that will centre on finding out the use of Nail Discolouration as a Screening Tool for Predicting low CD4 count in a Resource Limited Setting]
3. The interview process[getting a clearance, an interviewee, consent signing, questionnaire administration, physical examination and laboratory investigation]
4. Anonymity of contributor will be guaranteed

At all times, I will keep the source of the information confidential and refer to you or your words by a pseudonym or invented name which I would like you to choose. See name above. I shall keep any or the record of your participation locked away at all times, and destroy them after the data has been collected.

5. Things that may affect your willingness to participate

The interview may touch on issues which may affect your willingness to participate. If there is anything that you would prefer not to discuss, please feel free to say so. I will not be offended and there will be no negative consequences if you would prefer not to answer a question. I would appreciate your guidance should I ask anything which you see as intrusive.

6. Agreement

6.1 Interviewee's agreement

The respondent will be asked to give his consent in writing if possible

6.2 Interviewers agreement

I shall keep the consents of the above research interview confidential in the sense that the pseudonym noted above will be used in all documents which refer to the interview. The contents will be used for the purposes referred to above, but may be used for published or unpublished research at a later stage without further consent. Any change from this agreement will be renegotiated with you.

Signed (Peter Nnamdi Ekeh)

Date: 15/07/2009 Place: APIN CENTRE, JUTH

APPENDIX 3: Questionnaire

Survey on nail discoloration and correlation with CD4 cell count among untreated HIV positive patients.

Section A:

Demographic data

1. Patient unique ID: □□□□□□□□

2. Year of HIV diagnosis? _____

3. What is your sex? □Male=1 Female =2

4. What is your age (in years)? _____

5. What is your occupation? □Farmer=1, Civil servant =2, student=3, applicant =4 , business=5, others=6

6. What is your educational level? □None=1, Primary=2, Secondary =3, Post Secondary =4, others=5

7. Place of residence: □ Rural=1 Urban =2

Section B:

Clinical data

8. Do you have any medical complaint? □ Yes=1 No=2

9. If yes, what is it?_____

10. Duration of the medical complaints: □1= less than one month, 2= one to three months, 3=more than three months□

11. Have you been diagnosed of kidney problem in the past? □ Yes=1 No=2

12. Have you had your blood washed because of kidney problem (haemodialysis) in the past? □ Yes=1 No =2

13. Have you been diagnosed or treated with liver problem in the past? □Yes=1 No=2

14. Do you paint your fingernails? □Yes=1 No =2

15. Is your fingernail color changing past 7-10 years? □Yes=1 No =2□Don't know =9

16. Do you smoke cigarette? □Yes=1 No =2

17. Any past/present history of drug reaction/poisoning? □ 1= YES 2= NO

18. If yes, which one?_____

Examination

19. Fingernail discoloration: □NO=1 Distal banded=2 Grey=3 Indeterminate=4 others =5

20. General physical examination:_____1=normal 2=others

Laboratory investigations

21. Baseline CD4 cell count: _____

22. Baseline viral RNA level:_____

23. HBsAg Status: □positive=1 Negative=2

24. HCVAb Status: □positive=1Negative=2

25. Hemoglobin level:_____

26. Serum aspartate transaminase level (AST): _____

Normal: men up to 38 uL, Female: up to 32 Ul

27. Serum alanine transaminase level (ALT): _____

Normal levels: Men up to 41 Ul, Female: up to 31uL

28. Serum alkaline phospatase (ALP):_____

Normal levels: Men 40-129 u/L; Female 35-104 u/L

29. Serum bilirubin level (total): _____

Normal levels: adult up to 1.1mg/dL

30. Serum albumin: _____

Normal level: adult 3.4-4.8 g/dL

31. Total protein: _____

Normal level: adult 6.6-8.7u/l

31. Serum Urea Level: _____

Adults: 10-50 mg/dL

32. Serum Creatinine level:_____

Normal levels: Men 62-106 uMol/L; Female: 44- 80uMol/L

APPENDIX 4: JUTH IRB approval letter

JOS UNIVERSITY TEACHING HOSPITAL
JOS, NIGERIA

Phone: 073-450226 - 9
E-mail: juth@infoweb.abs.net

Cables & Telegram: JUTH
P.M.B 2076
Jos.

Ref: JUTH/DCS/ADM/127/XIX/2756

Date: 22nd March 2010

Dr. Ekeh Peter Nnamdi,
APIN Laboratory,
JUTH, Jos.

RE: ETHICAL CLEARANCE/APPROVAL

I am directed to refer to your application dated 20th February 2010 on the research proposal titled: "***Survey on nail discoloration and association with CD4 count among untreated HIV patients***" and your appearance before the Ethical Committee.

Following recommendation from the Institutional Health Research Ethical Committee, I am to inform you that Management has given approval for you to proceed on your research topic as indicated.

You are however required to obtain a separate approval for use of patients and facilities from the department(s) you intend to use for your research.

The Principal Investigator is required to send a progress report to the *Ethical Committee* at the expiration of three (3) months after ethical clearance to enable the Committee carry out its oversight function.

Submission of final research work should be made to the Institutional Health Research Ethical Committee through the **Secretary in Room 14, Administration Department**, please.

On behalf of the Management of this Hospital, I wish you a successful research outing.

Hajia R. Danfillo
for: *Chairman, MAC*

INSTITUTIONAL HEALTH RESEARCH
ETHICAL COMMITTEE
DESPATCHED
24 MAR 2010
JOS UNIVERSITY TEACHING
HOSPITAL, P.M.B 2076 JOS

APPENDIX 5: APIN clinic permission

APIN CENTRE

Jos University Teaching Hospital

30th April, 2010

DR EKEH PETER NNAMDI

APIN Centre,

Jos University Teaching Hospital,

Jos.

RE: Request for Use of Adult Antiretroviral Clinic Patients & Facilities for My Thesis

I am directed to refer to your application dated 29th April, 2010 to access patients' data to carry out a research for your thesis for a Masters in Public Health for which you have obtained ethical clearance and approval from the JUTH Ethical Committee.

This is to inform you that APIN, JUTH Management has given approval for your application to carry out the research on *"Survey on Nail Discoloration and Association with CD4 Count among Untreated HIV patients"* at the APIN Centre, JUTH, Jos.

You are however to note that no part of the data gathered from the research should be published without prior approvals from the APIN, JUTH, Jos and Harvard School of Public Health, Boston.

On behalf of the management, I wish you a fruitful research.

Alechenu Emmanuel O.

for Principal Investigator

APIN PLUS/HARVARD
DESPATCHED
30 APR 2010
SIGN
JUTH, JOS

Cc:

Site Coordinator, APIN, JUTH
Data Manager, APIN, JUTH
Research Coordinator, APIN, JUTH

In collaboration with Harvard School of Public Health, Boston USA

2 Murtala Moh'd Way, Jos.Plateau State, Nigeria, E- Mail:apinjos@yahoo.com
234 73 - 450226 -9 ext. 2451

APPENDIX 6: CITI Collaborative Institutional Training Initiative

CITI Collaborative Institutional Training Initiative

Basic Course - Human Subjects Research Curriculum Completion Report
Printed on 8/5/2010

Learner: PETER NNAMDI EKEH (username: petekiae)
Institution: CITI Demo for WHO / PAHO
Contact Information Jos, Plateau 93001 Nigeria
Department: Internal Medicine
Phone: +2348027056425
Email: petekiae@yahoo.com
Biomedical Research:

Stage 1. Basic Course Passed on 05/27/10 (Ref # 4458818)

Elective Modules	Date Completed	Score
Introduction	05/26/10	no quiz
Belmont Report and CITI Course Introduction	05/26/10	1/3 (33%)
History and Ethical Principles	05/26/10	7/7 (100%)
Basic Institutional Review Board (IRB) Regulations and Review Process	05/26/10	4/5 (80%)
Informed Consent	05/26/10	4/4 (100%)
Social and Behavioral Research for Biomedical Researchers	05/26/10	3/4 (75%)
Records-Based Research	05/26/10	2/2 (100%)
Genetic Research in Human Populations	05/26/10	2/2 (100%)
Research With Protected Populations - Vulnerable Subjects: An Overview	05/26/10	3/4 (75%)
Vulnerable Subjects - Research with Prisoners	05/26/10	3/4 (75%)
Vulnerable Subjects - Research Involving Minors	05/26/10	2/3 (67%)
Vulnerable Subjects - Research Involving Pregnant Women and Fetuses in Utero	05/27/10	3/3 (100%)
International Research	05/27/10	1/1 (100%)
Group Harms: Research With Culturally or Medically Vulnerable Groups	05/27/10	2/3 (67%)
FDA-Regulated Research	05/27/10	4/5 (80%)
Human Subjects Research at the VA	05/27/10	2/3 (67%)
HIPAA and Human Subjects Research	05/27/10	2/2 (100%)
Workers as Research Subjects-A Vulnerable Population	05/27/10	4/4 (100%)
Hot Topics	05/27/10	no quiz
Conflicts of Interest in Research Involving Human Subjects	05/27/10	1/2 (50%)

CITI Collaborative Institutional Training Initiative

Good Clinical Practice Curriculum Completion Report
Printed on 8/5/2010

Learner: PETER NNAMDI EKEH (username: petekiae)
Institution: CITI Demo for WHO / PAHO
Contact Information Jos, Plateau 93001 Nigeria
Department: Internal Medicine
Phone: +2348027056425
Email: petekiae@yahoo.com

Good Clinical Practice and ICH:

Stage 1. Basic Course Passed on 05/28/10 (Ref # 4465512)

Elective Modules	Date Completed	Score
GCP Introduction	05/27/10	2/3 (67%)
Overview of New Drug Development	05/27/10	5/5 (100%)
International Conference on Harmonisation (ICH): GCP Requirements	05/27/10	2/4 (50%)
FDA Regulated Research and ICH for Investigators	05/27/10	4/5 (80%)
International Conference on Harmonisation - ICH for Investigators	05/27/10	no quiz
Conducting Investigator-Initiated Studies According to FDA Regulations and Good Clinical Practices	05/27/10	3/3 (100%)
Investigator Obligations in FDA-Regulated Clinical Research	05/28/10	3/5 (60%)
Managing Investigational Agents According to GCP Requirements	05/28/10	4/5 (80%)
Conducting Clinical Trials of Medical Devices	05/28/10	3/3 (100%)
Informed Consent-An Ongoing Process	05/28/10	4/4 (100%)
Detection and Evaluation of Adverse Events	05/28/10	4/4 (100%)
Reporting Serious Adverse Events	05/28/10	3/4 (75%)
Audits and Inspections in Clinical Trials	05/28/10	5/5 (100%)
Monitoring of Clinical Trials by Industry Sponsors	05/28/10	7/8 (88%)
Completing the CITI GCP Course	05/28/10	no quiz

CITI Collaborative Institutional Training Initiative (CITI)

Responsible Conduct of Research Curriculum Completion Report
Printed on 8/5/2010

Learner: PETER NNAMDI EKEH (username: petekiae)
Institution: CITI Demo for WHO / PAHO
Contact Information Jos, Plateau 93001 Nigeria
Department: Internal Medicine
Phone: +2348027056425
Email: petekiae@yahoo.com

Biomedical Responsible Conduct of Research Course.:

Stage 1. Basic Course Passed on 05/31/10 (Ref # 4465511)

Elective Modules	Date Completed	Score
The CITI Course in the Responsible Conduct of Research	05/28/10	no quiz
Introduction to the Responsible Conduct of Research	05/28/10	no quiz
Research Misconduct 1-1215	05/28/10	4/5 (80%)
Case Study - Truth or Consequences 1-1470	05/28/10	2/3 (67%)
Case Study Plagiarism 1-1473	05/28/10	2/2 (100%)
Case Study No News Is Not Good News - 1-1469	05/28/10	3/3 (100%)
Data Acquisition, Management, Sharing and Ownership 1-1308	05/28/10	5/5 (100%)
Case Study - Data Management - Share and share Alike 1-1199	05/28/10	3/3 (100%)
Case Study - Data Management "Who Owns Research Data?" 1- 1444	05/28/10	3/3 (100%)
Case Study - Data Management "The New Clinical Data Manager" BioMed 12-1201	05/28/10	no quiz
Publication Practices and Responsible Authorship 1-1380	05/28/10	3/5 (60%)
Responsible Authorship - The Chair as an Author. 1-1320	05/29/10	2/2 (100%)
Authorship and Publications -The Grateful Author 1-1235	05/29/10	5/5 (100%)
Peer Review 1-1368	05/29/10	5/5 (100%)
What is Responsible Peer Review 1-1369	05/29/10	5/5 (100%)
Peer Review and Controversial Research 1-1375	05/29/10	2/3 (67%)
Mentor and Trainee Responsibilities 01234 1250	05/29/10	4/6 (67%)
Mentoring Case Study: O, What a Tangled Web We Weave.	05/29/10	4/4 (100%)
Mentoring Case Study: The Graduate Student Laborer.	05/29/10	3/3 (100%)
Mentoring Case Study: Sherry's Secret.	05/29/10	4/4 (100%)

Mentoring Case Study: Lisa Bach's Case	05/30/10	2/3 (67%)
Mentoring Case Study: The Business of Mentoring.	05/30/10	3/4 (75%)
Mentoring Case Study: Too Much Help is Just Too Much!	05/30/10	2/3 (67%)
Conflicts of Interest and Commitment 1-1622	05/30/10	4/6 (67%)
CoI Case Study The Case of the Promising New Technology 1-1220	05/30/10	3/4 (75%)
CoI -The Case of the Entrepreneurial Clinician 2-1451	05/30/10	4/5 (80%)
CoI Case Study - Janet's Suspicions 1-1245	05/30/10	3/3 (100%)
CoI Case Study - Cain and Abel4-1453	05/30/10	3/3 (100%)
Collaborative Research 1-1450	05/31/10	6/6 (100%)
Collaborative Research Simulation - 8 Scenarios and resolutions	05/31/10	no quiz
When Collaborators Become Competitors 1-1182	05/31/10	2/3 (67%)
When Collaborators Disagree 1-1391	05/31/10	2/3 (67%)
Why Can't We All Just Get Along 1-1396	05/31/10	3/3 (100%)
Collaborations Between Academics 1-1394	05/31/10	4/4 (100%)
Marriage Has It's Advantages 1-1404	05/31/10	2/2 (100%)
The Price of Collaboration	05/31/10	no quiz
A Possible Co-Author	05/31/10	no quiz
Supporting Documentation	05/31/10	no quiz
Facilitating Sharing Between Collaborators	05/31/10	no quiz
The CITI RCR Course Completion Page.	05/31/10	no quiz

For this Completion Report to be valid, the learner listed above must be affiliated with a CITI participating institution. Falsified information and unauthorized use of the CITI course site is unethical, and may be considered scientific misconduct by your institution.

Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

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