MUCOCUTANEOUS DISORDERS AMONG HIV/AIDS ADULT PATIENTS WITH ANTI-RETROVIRAL TREATMENT FAILURE ATTENDING AMTULABHAI KARIMJEE CARE AND TREATMENT CLINIC IN DAR ES SALAAM

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By

Pamela Fredrick Kaaya

A Dissertation/ Thesis Submitted in (partial) Fulfillment for the Requirements for the Degree of Master of Medicine (Internal Medicine) of Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Sciences a thesis/ dissertation entitled *Mucocutaneous Disorders among HIV/ AIDS Adults Patients with Anti-Retroviral Treatment Failure Attending Amtulabhai Karimjee Care and Treatment Clinic in Dar es Salaam* in (Partial) fulfillment of the requirements for the degree of Master of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied Sciences.

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Dr. Yassin Mgonda

(Supervisor)

Date: _____

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Prof. Muhammad Bakari

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Date: _____

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I, **Pamela Fredrick Kaaya** declare that this **dissertation/ thesis** is my own original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

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Glory, praise and honors are to GOD for taking me through this work and my studies. AMEN.

ABSTRACT

Background: Majority of HIV infected individuals present with one or more cutaneous disorders during the course of their HIV infection and may present at treatment failure. Treatment failure in developing countries is on the rise; however, scanty literature exists on mucocutaneous disorders in patients with ART failure.

Objective: To determine the pattern of mucocutaneous disorders among HIV/AIDS patients with treatment failure attending Amtulabhai Karimjee Treatment failure Clinic (AKC) in Dar es Salaam.

Study design and settings: A clinic – based descriptive cross sectional study was conducted among HIV patients with ARV treatment failure attending Amtulabhai Karimjee Treatment failure Clinic.

Materials and Methods: All patients referred to AKC were scrutinized to ascertain their ARV treatment failure status. Patients with treatment failure were then consecutively recruited into the study after obtaining their written consent to achieve the required sample size. Appropriate clinical information obtained through history and complete dermatological examination was recorded into a specially designed questionnaire. Blood sample was taken for the determination of CD4+ T-Lymphocytes count by Flowcytometry. Dermatological diagnoses were made based on observed clinical features and in doubtful cases assistance was sought from a Dermatologist. Investigations including skin biopsies were taken where indicated. Digital photographs were taken where necessary for discussion with a Dermatologist. Data was analyzed using SPSS, and Chi squared test was used to compare proportions.

Results: Two hundred and forty six subjects were enrolled into the study, of whom 154 (62.6%) were females. The overall mean age was 40.5 (SD±10.5) years. The age ranged from 19 to 73 years. The overall prevalence of one or more mucocutaneous disorder was 52.8%.

There was a striking female preponderance of patients with mucocutaneous disorders 94/130 (72.3%). The elderly (>47 years) were the least affected 27/66 (40.9%) compared to the age groups (19 – 32 years) who were most affected 32/51(62.7%. Inflammatory/ papulosquamous disorders ranked highest, with an overall prevalence of 79/130 (60.8%). Pruritic Papular Eruption (PPE) was the commonest of these, having a prevalence of 71/130 (54.6%). Females had three times the prevalence of PPE compared to males.

Seborrhoeic dermatitis and Eczema were each prevalent in 3/130 (2.3%) of patients. Lichenoid hypersensitivity reaction and lichen simplex chronicus were the least common.

Infectious diseases had a prevalence of 64/130 (49.2%). Of these, fungal infections were most predominant being present in 31/130 (23.8%) of patients. Viral infections had a prevalence of 30/130 (23.0%).

Malignant conditions were rare, being encountered in 3 patients only; 2 with sarcoma, and 1 with squamous cell carcinoma,

Among the 130 patients, 80.8% had one type of mucocutaneous disorder; while 19.2% had 2 or more types mucocutaneous disorders.

Of those patients with CD4 count less than 200 cells/µl, PPE was encountered more frequently 60/120 (50%) compared to other mucocutaneous disorders, p=0.003. The mean CD4 count of patients with PPE was 166.1 cells/µl.

Conclusion:

- Majority of patients with treatment failure were females
- Mucocutaneous disorders were a common presentation in patients on treatment failure
- Chronic persistent PPE was the most frequent mucocutaneous disorder finding
- More then two third of the mucocutaneous disorders presented at the CD4 T cell counts less than 200 cells/µl

Recommendation

In view of the high frequency of mucocutaneous disorders in patients with treatment failure, Clinicians should be sensitized to perform a thorough dermatological examination in each patient. Presence of PPE should increase the index of suspicion for ARV failure

LIST OF ABBREVIATIONS

AIDS	-	Acquired immunodeficiency syndrome
ART	-	Anti retroviral therapy
ARV	-	Anti retroviral
AZT	-	Zidovudine
CD4	-	Cluster of differentiation-4
CMV	-	Cytomegalovirus
CTC	-	Care and treatment clinic
D4t	-	Stavudine
Ddi	-	Didanosine
EFV	-	Efavirenz
HAART	-	Highly active antiretroviral therapy
HIV	-	Human immuno deficiency virus
IRIS	-	Immune reconstitution inflammatory syndrome
MOH	-	Ministry of Health
MOHSW	-	Ministry of Health and Social Welfare
NNRTI	-	Non-nucleoside reverse transcriptase inhibitor
NRTI	-	Nucleoside reverse transcriptase inhibitor
NVP	-	Nevirapine
PI	-	Protease inhibitor
PPE	-	Pruritic papular eruption
PVL	-	Plasma viral load
WHO	-	World Health Organization
3TC	-	Lamivudine

TABLE OF CONTENTS

1.0 INTRODUCTION

Since the advent of anti retroviral therapy patients have been experiencing treatment failure due to several reasons and its predictions have been largely researched and clearly outline[1] It is well documented that patients with HIV/AIDS will experience mucocutaneous disorders at some stages of their HIV infection. However to date little if any data exists on mucocutaneous disorders findings among patients with treatment failure. The aim of this study was to determine the pattern of mucocutaneous disorders among HIV/AIDS patients with treatment failure attending Amtulabhai Karimjee Treatment failure Clinic (AKC) in Dar es Salaam.

2.0 LITERATURE REVIEW

HIV/AIDS remains a global problem bearing a heavier burden in developing countries though recently trend of new HIV infection is declining. In sub- Saharan Africa, where the majority of new HIV infections continue to occur, and estimated 1.8 million (1.6 million–2.0 million) people became infected in 2009. Considerably lower than the estimated 2.2 million (1.9 million–2.4 million) people in sub-Saharan Africa newly infected with HIV in 2001.[2] This slight decrease in prevalence can be explained by improved access to ARV treatment. This is also evidenced by the 18% decline in annual HIV related mortality observed in the region since 2004. Despite these ongoing efforts Sub-Saharan Africa remains the region most heavily affected by HIV. In 2008 it accounted for 67% of HIV infections world-wide, 68% of new infections among adults and 91% among children. An estimated 1.4 million AIDS related deaths occurred in 2008, accounting for 72% of the world's AIDS related deaths.[3]

In Tanzania efforts to curb the pandemic have not gone unnoticed. Earlier reports by NACP (2003 and 2006) revealed a national prevalence of 11% and 7% respectively; showing a decline in prevalence over the years.[4]

1.1 Mucocutaneous manifestations of HIV/ AIDS

More than 90% of HIV infected individuals present with one or more cutaneous manifestations during the course of their HIV infection[5]. Skin conditions are frequently initial signs of immunosuppresion and may indicate progression of HIV disease. They can also be disabling, disfiguring or even life – threatening.[6]

Mucocutaneous manifestations often influence the general health status and indicate a worse prognosis of the disease. Several studies have shown that the association of skin disorders with HIV infection can serve as diagnostic factors as well as indicators for advanced HIV infection, immunosuppression and decreased CD4 T cell counts.[7,8,9,10]

Acute primary infection may lead to a transient, generalized morbilliform eruption on the trunk. With the onset of immunosuppression, nonspecific skin changes may occur. These may include recurrent Herpes simplex infection, varicella zoster, numerous hyperkeratoic warts, treatment resistant seborrhoeic dermatitis and oral hairy leukoplakia.[11]

In the later stages of HIV disease, molluscum contagiosum and cytomegalovirus (CMV) may appear. Mycobacterial infection, mucocutaneous candidiasis and cutaneous malignancies e.g. Kaposi sarcoma and Non-Hodgkin's lymphoma may also occur.[12] Notable AIDS –defining skin markers that have high positive predictive value include Kaposi sarcoma, oral hairy leukoplakia, cutaneous cryptococcosis and oropharyngeal candidiasis whereas those warranting a high index of suspicion include conditions like herpes zoster, pruritic papular eruption (PPE), extragenital molluscum contagiosum in an adult, seborrhoric dermatitis, recurrent and extensive herpes simplex infection, Norwegian scabies, Steven's Johnson syndrome, large condylomas and extensive plane warts. Furthermore, the presence of an STI, particuraly genital warts and genital ulcers, increase the clinical suspicion of presence of HIV/ AIDS.[13] Other HIV related skin conditions may erupt or worsen due to the presence of HIV which may also act as a triggering factor.

In general, declining immunity is associated with increased number and severity of skin disorders.[11] Mucocutaneous disorders like vaginal candidiasis and herpes zoster occur early in HIV infection while Kaposi's sarcoma is common in advanced HIV infection. The advent of HAART has changed the spectrum of skin disorders by improving host immunity, which in turn reduces the occurrence of some of the above skin conditions.[12] However, the restoration of immunity may cause flare –up of herpes zoster, herpes simplex virus type 1 and 2, kaposi sarcoma-associated herpes virus or human herpes virus type 2 and molluscum contagiosum Maniar et al from Mumbai, India encountered candidiasis, Addisonian pigmentation, herpes simplex, hair changes, oral hairy leukoplakia and icthyosis among these are the commonest mucocutaneous markers of HIV seen.

1.2 Treatment of HIV/AIDS:

Highly active antiretroviral therapy for treatment of HIV infection has led to profound reductions in the incidence of mortality due to AIDS-related causes in recent years. HIV/AIDS is of paramount public health concern and efforts to arrest the pandemic continue to increase. Increased availability of ART here in resource limited settings has shown remarkable improvement in the health and survival of HIV –infected persons. The currently existing and commercially available antiretroviral drugs fall into the following 5 main categories

Binding Fusion inhibitors e.g. (Enfuvirtide)

    (a) Reverse Transcriptase inhibitors

        This group of drugs is further subdivided into:

        i.   Nucleoside reverse transcriptase inhibitors (NRTI)

              Eg. Zidovudine (AZT)

        ii.   Non-nucleoside reverse transcriptase inhibitors (NNRTI)

              Eg Nevirapine (NVP)

(b) Nucleotide Reverse Transcriptase Inhibitors (Nucleotide analogues) e.g. Tenofovir (TDF)

(c) Intergrase Inhibitors e.g. S-1360 are under investigation.

(d) Protease Inhibitors (PIs)eg. Lopinavir (LPV)

The ARV drugs mentioned above target different stages of the viral replication cycle (summarized below) inhibiting further viral multiplication. The various steps of the viral replication cycle serve as windows for intervention directed at one or several of the stages essential for viral replication.
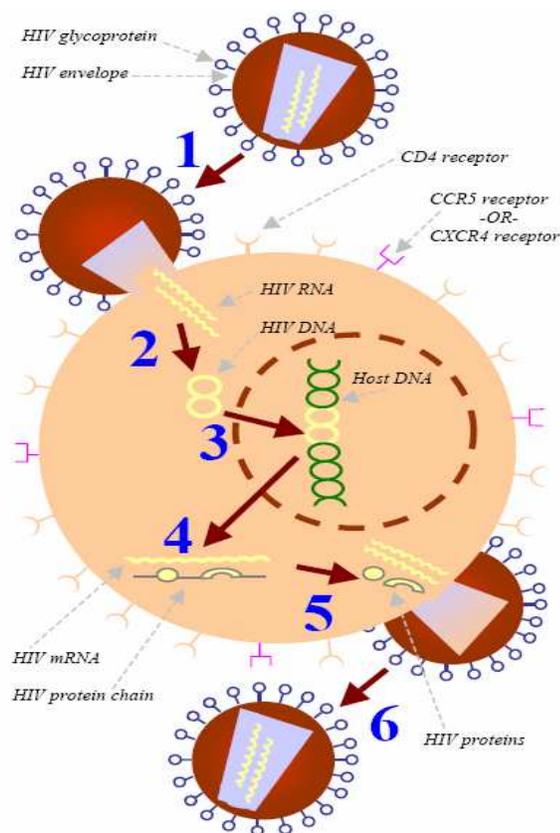
Key:

1. Binding and Fusion
2. Reverse Transcription
3. Integration
4. Transcription
5. Assembly
6. Budding

Figure 1: HIV REPLICATION CYCLE

Source: *AIDS info* U.S. Department of Health and Human Services

1.3 Recommended antiretroviral drugs in Tanzania:

ART naive patients and those who have received treatment before require a combination of drugs. Triple therapy consisting of 2NRTI + 1NNRTI, or 2NRTI+ 1PI or 3NRTI's is recommended.

The Ministry of Health and Social Welfare (MOHSW) recommends the following drugs as first line ARV combination regimen for adults and adolescent ART naïve patients.

(A) For first line treatment in Tanzania:

(i) Zidovudine (AZT) (v) Tenofovir (TDF)

(ii) Stavudine (d4T) (vi) Nevirapine (NVP)

(iii) Lamivudine (3TC) (vii) Efavirenz (EFV)

(iv) Emtricitabine (FTC)

(B) Second –line ARV regimen in Tanzania:

NRTI's   ▪ Abacavir (ABC)

　　　　　▪ Didanosine (DDI)

　　　　　▪ Tenofovir with Lamivudine or Emtricitabine (TDF + 3TC or FTC)

PIs   ▪ Lopinavir boosted by Ritonavir (LPV/r)

　　　▪ Atazanavir boosted by Ritonavir (ATR/r

Clinical and Immunological effects of HAART

Researchers have looked in detail at the effect of HAART on the CD_4 count of people treated with ARV's and observed a variety of CD4 count responses. However, the most common pattern is for people to experience dramatic increases in their CD_4 count in the first few months of treatment followed by a more gradual increase during the following months and

years.[14] This has remarkably reduced the incidence of opportunistic infections in HIV patients. Some patients who have been started on HAART (a minority of patients) do present with the so-called "paradoxical response" defined as a discrepancy between the plasma viral load (PVL) and the $CD_{4\,T}$ cell count. The first situation occurs in 7-15% of patients. The CD_4 T cell count rises despite a persistently detectable PVL. The second type of paradoxical response occurs in 5 – 15% of patients. The CD_4 T cell count does not rise despite a fully suppressed viral growth and disappearance of opportunistic infections.[15] Resolution of sarcoma has been found to occur with 1.3 log reduction in viral load and clearance of intractable molluscum contagiosum with a coincident ten-fold rise in CD4 cells.

Cutaneous morbidity was markedly reduced in patients who received a combination of regimens that included protease inhibitors (PI's) than those treated with nucleoside analogues only.[16] A study done in the Department of Dermatology and Venereology at the university of Essen, Germany (Hengge et al. 2000) observed that infectious dermatological diseases such as candidiasis, dermatophyte infection, folliculitis, sarcoma, recurrent Herpes simplex virus infection and oral hairy leukoplakia showed some dramatic decrease in HIV/AIDS-infected patients after initiation of HAART while some infections such as papilloma virus and mollusca infections increased in prevalence. Herpes zoster occurred more frequently after HAART, which they attributed to an inflammatory immune reaction. Non-infectious skin conditions such as dry skin and pruritus, which were highly prevalent before the introduction of HAART, did not change significantly. They attributed this result to the fact that the occurrence of these conditions was unaffected by the strengthened immune system because of the lack of an infectious cause and that protease inhibitors have been shown to produce pruritus and skin dryness as adverse side-effects.

1.4 HIV mucocutaneous manifestations and ARV responses

Mucocutaneous manifestations in HIV infected individuals exhibit varied responses to anti retro viral therapy, some may show a marked decline in their frequency with the initiation of ARVs while others may remain unchanged. Conditions like psoriasis, prurigo nodularis, molluscum, photodermatitis and drug reactions which are more prone to occur at lower CD4 T cell levels (below 200/µl) tend to improve with adequate Anti retro viral treatment and immune reconstitution.[17]

1.5 Treatment failure in HIV/AIDS patients:

Several factors have been found to be associated with treatment failure. These include, viral resistance, low baseline cd4 T cell count of less than 100 cell/µl, a higher baseline viral load and non adherence to HAART regimens.[18,19,20,21,22]

Patients who are not linked to home based care and those who don't disclose their HIV status to their family members have been associated with poor adherence and as a result end up with treatment failure more often than not. Adherence of more than 95% is associated with viral load suppression of 81%, however 90-95% adherence will be associated with a viral suppression of 64%, 80-90% adherence with a suppression of 25% and adherence of less than 70% will suppress only 6%. [23] For treatment to be successful, ARV medication must be taken at least 95% of the time.[24]

Although there has been significant progress in HIV care since the advent of HAART, therapies continue to fail in a large number of cases, this being due to resistance which is basically or primarily driven or caused by sub-optimal adherence. Prevalence of treatment failure globally occurs in 30% of patients on HAART.[25]

This prevalence varies between continents; a study in Uganda in East Africa reported the prevalence of immunological failure to be 38% whereas in North America, the reported prevalence was 12%.[26]

In Tanzania and other countries in sub Saharan Africa, HIV/ AIDS patients are at a higher risk of developing treatment failure due to poor adherence which constitutes a serious challenge to those receiving ART.[27,28] Regimens are often complicated and can include varying dosing schedules and can be associated with serious adverse affects.

Monitoring of HIV treatment can be done by using clinical, immunological and virological criteria. In Tanzania and other developing countries treatment response can be monitored mainly on clinical and immunological parameters. However in light of declining costs of performing viral load measurements along with a simplification process, where available, viral load parameters should also be applied. Furthermore, clinical failure is associated with failing CD4 counts and IRIS associated with improvement in immune response i.e. CD4 counts

Definition of treatment failure according to Tanzania national guidelines for the management of HIV/AIDS 2008:
Treatment failure may be categorized as:
    (i) Clinical treatment failure
    (ii) Immunological treatment failure
    (iii) Virological treatment failure

Clinical treatment failure
 This is said to have occurred when there is disease progression with clinically stage 4 opportunistic infections or malignancy occurring 6 months or more after initiation of ART.

Immunological treatment failure

This is defined as a fifty percent drop in CD4 T cell count from peak value within 6 months or return to pre ART baseline CD4 T cell count or lower. The CD4 T-cell count (or CD4 count) serves as the major clinical indicator of immunocompetence in patients with HIV infection. It is usually the most important consideration when deciding to initiate or change antiretroviral therapy in the case of treatment failure. The most recent CD4 T cell count is the strongest predictor of subsequent disease progression and survival according to clinical trials and cohort studies data on patients receiving antiretroviral therapy.

Virological treatment failure:

This is divided into primary and secondary virological failure:

- Primary, if there is less than a 10 fold drop in viral load after 6-8 weeks of therapy, or when the viral load (VL) is persistently above 10,000 copies/ul.
- Secondary, if there is a 10 fold increase in viral load from lowest recorded level.

Immunological and Virological evaluations

In general, CD4 T cell count levels should be determined every 3 to 6 months to:

1. Determine when to start antiretroviral therapy in patients who do not meet the criteria for initiation.
2. Assess immunologic response to antiretroviral therapy.
3. Assess the need for initiating chemoprophylaxis for opportunistic infections.
4. Assess the need for change of antiretroviral drug to other in the case of treatment failure.

Plasma HIV RNA (viral load) may be a consideration in the decision to initiate therapy. In addition, viral load is critical for evaluating response to therapy including treatment failure. Three HIV viral load assays have been approved for clinical use:

1. HIV-1 reverse transcriptase polymerase chain reaction (PCR) assay (Amplicor HIV-1 Monitor Test, version 1.5, Roche Diagnostic)
2. Nucleic acid amplification test for HIV RNA (NucliSens HIV-1 QT, bioMerieux).
3. Signal amplification nucleic acid probe assay (VERSANT HIV-1RNA 3.0 assay, Bayer).

Thus, viral load testing serves as a surrogate marker for treatment response and may be useful in predicting clinical progression. The minimal change in viral load considered to be statistically significant (2 standard deviations) is a threefold or a 0.5 log10 copies/Ml change. Information on magnitude of treatment failure is lacking in many centers in Tanzania and Africa in general.

2.0 PROBLEM STATEMENT

Skin conditions are highly prevalent in HIV/ AIDS patients and may occur at all stages of HIV infection. The initiation of HAART suppresses HIV replication which results in rapid and sustained rises in absolute $CD4^+$ T-cell count.[13] while the infectious poll shows contrasting responses some exhibiting decrease in prevalence and others increase, the non –infectious pole remains without significant change.

Some mucocutaneous disorders have decreased markedly due to potent antiretroviral therapy, other conditions remain common. Among patients with low $CD4^+$ T-cell counts who are not on or not adherent to antiretroviral therapy, notable conditions include psoriasis, photodermatitis, prurigo nodularis, molluscum and adverse drug reactions. Conditions that remain relatively common despite adequate antiretroviral therapy include eczema, xerosis, warts and Kaposi's sarcoma.

Ongoing efforts to increase access to ARV in resource limited settings can be appreciated and these are now relatively widely available to patients, however, a number of patients are

experiencing treatment failure. Moreover, monitoring of ARV treatment mainly relies on clinical and immunological parameters and even the latter is sometimes limited especially in remote areas. Viral load screening remains costly and not widely available and hence reserved for a minority of cases. Hence the diagnosis of treatment failure still poses a major challenge to clinicians and is possibly often under diagnosed. As HIV/AIDS patients with mucocutaneous disorders experience varying responses to ART, presentations may also be diverse in treatment failure. This is widely unresearched and data is lacking.

3.0 STUDY RATIONALE

Patients once commenced on ARV therapy require careful and regular monitoring clinically and immunologically, and this is even more so in a country like Tanzania, where treatment options are limited, and factors such as poor adherence present a major drawback of treatment success. Such careful monitoring is a big challenge to clinicians due to lack of adequate facilities (e.g. Machines and reagents to measure viral load and $CD4^+$ T-cell counts)

Skin manifestations have been proven to be indicators of HIV/AIDS infection and have prompted early diagnosis and treatment by increasing the index of suspicion of infection .To date however, scanty if any literature exists on the role of skin manifestation as predictors of treatment failure hence the need to study and document this. Data obtained from the study may serve to alert clinicians on the progress of treatment as well as similarly increase the suspicion index for treatment failure.

4.0 OBJECTIVES

4.1 Broad objective

To determine the pattern of mucocutaneous disorders among HIV/AIDS patients with treatment failure attending Amtulabhai Karimjee Treatment failure Clinic (AKC) in Dar es Salaam.

4.2 Specific objectives:

i.   To determine the social demographic characteristics of HIV/AIDS patients with treatment failure attending the Amtulabhai Karimjee ART Treatment failure clinic in Dar es Salaam.

ii. To determine the prevalence of mucocutaneous disorders among HIV/AIDS patients with treatment failure attending Amtulabhai Karimjee Treatment failure clinic in Dar es Salaam.

iii. To determine the types of the mucocutaneous disorders among HIV/AIDS treatment failure patients attending Amtulabhai Karimjee Treatment failure clinic in Dar es Salaam

iv. To determine the mean $CD4^+$ -T cell counts of HIV/AIDS patients treatment failure patients with mucocutaneous disorders attending Amtulabhai Karimjee Treatment failure clinic in Dar es Salaam

5.1 Study design:

This was a descriptive cross –sectional study.

5.2 Study period:

June 2010- September 2010

5.3 Study area:

The study was conducted at AMTULABHAI KARIMJEE TREATMENT FAILURE CLINIC (AKC).This is a Care and Treatment facility supported by HAVARD-PEPFAR collaborative services located in Mnazi Mmoja in Ilala district, Dar es Salaam. The clinic started operating effectively from August 2009 and runs 5 days a week operating from Monday to Friday, 7:30am to 6:30pm, Friday being set aside for children.

This clinic caters for all patients with treatment failure referred from different sites of which there are 29, all located within the 3 district hospitals as well as in all the health centers of Dar es salaam. Currently it has a total of 842 patients; 153 children, 689 adults (252 males, 437 females). In a week they receive between 2 and 3 new cases. Also the number of follow up adult patients that are seen during the week is about 400.

5.4 Sample size determination:

The sample size was obtained using the following formula.

Sample size;

$$n = \frac{NZ^2 pq}{(N-1)e^2 + pqZ^2}$$

        n = sample size

        Z = % point corresponding to a significant level of 5% = 1.96

        P = Prevalence of patients with treatment failure with a dermatological disorder was assumed to be (50%)

        $q = 1 - P$

        e = maximum likely error (5%)

        When p=q=50%=0.5 the formula simplified to;

$$n = \frac{NZ^2}{4(N-1)e^2 + Z^2}$$

$$n = \frac{689 \times 1.96^2}{4 \times 688 \times 0.05^2 + 1.96^2}$$

$$n = 246$$

5.5 Study subjects:

All adults (18 and above) HIV/AIDS patients on ARV treatment for more than six months and diagnosed with Immunological and Virological treatment failure, as defined by Ministry of Health and Social Welfare, National Guidelines for management of HIV and AIDS.

5.3.1 Inclusion criteria:
- All HIV/AIDS patients (18yrs and above of either sex) categorized as treatment failure, attending AKC Dar es Salaam
- Patients with proper follow up records of their CD4 T cell counts profiles and viral load profiles
- Those consenting to take part in the study

5.3.2 Exclusion criteria:
- Patients on immunosuppressive treatment
- Patients with incomplete medical records
- Patients with a congenital cutaneous disorder
- Patients showing improvements with 2nd line ARVs

5.6 Patient Recruitment and Study procedure:

5.6.1 Patient recruitment

Patients referred to AKC were selected from the attendance list of that particular clinic day. The researcher selected a patient after an interval of every two patients on the list. Then each selected patient was accessed to meet the inclusion criteria. If he/she met the criteria, he/she was then consecutively recruited into the study after obtaining their written consent to achieve the required sample size. All necessary information concerning the study was explained to the participants.

5.6.2 Study procedure

Clinical intervention

Using a questionnaire that was specifically designed for this study, patients were interviewed and their information recorded. This included demographic data (i.e. Age, sex, tribe, marital status, and occupation), HIV and ARV history, presence or no of skin lesions as well as treatments used. After an interview each participant underwent a complete dermatological examination and the type of mucocutaneous disorder recorded on a data collection sheet. The dermatological examinations were carried out by a researcher who attended a short training on physical examinations and diagnosis of common mucocutaneous conditions in HIV/AIDS patients. In doubtful or complicated cases patients were ferried to the Dermatology clinic at MNH for discussion with Consultant Dermatologist. Where necessary digital photographs were also taken for later discussion with the Dermatologist.

Dermatological diagnosis

Dermatological diagnoses were established clinically basing on through history which was followed by a complete dermatological examination in appropriate light with patient fully undressed .where necessary laboratory tests were performed. In this study most of the dermatological diagnoses were done clinically only in few lesions histological tests were done.

Histology

Tissue samples from representative sites including normal margins were taken, preserved in 10% formalin and sent to the pathology department for histological diagnosis /confirmation.

Data processing and analysis

All data were entered into a computer and cleaned to ensure accuracy of all entries. Analysis was done using version 13.0 a chi squared test was employed to compare categorical variables.

5.7 Ethical consideration

Ethical clearance was obtained from the Research and Publications Committee of Muhimbili University of Health and Allied Sciences (MUHAS), and the Ilala District Medical Officer respectively.

A written consenting form was prepared in Swahili language. After an informed-consent statement was read out, the written informed consent was obtained from all study participants.

In addition to consenting, individual participants were informed of their anonymous data use. For strict confidentiality and adherence, none of the participants' names appeared on the questionnaires on account that all questionnaires were separately coded. A unique study identification code was assigned to each subject and the data accessed by the investigator/ supervisor and/ or research group.

All patients continued to receive care and treatment irrespective of their participation in the study. Patients with dermatological diagnosis were explained about their diagnosis and offered treatment by the investigator.

6.0 RESULTS

A total of 246 patients were recruited to participate in the study, of these, 154 (62.6%) were females. The overall mean age was 40.5(SD±10.5). Their ages ranged between 19 and 73 years with the largest group comprising of adults in the age group of 33-46 years (52.4%) followed by 47 years and above (26.8%).

Most of the participants (70.7%) were employed, while students formed the smallest group (3.3%). Overall, 90/246 (36.6%) were married, while single patients were 70 (28.5%). Forty three patients were widowed. The least group comprised of cohabitants, 7 (2.8%). The majority of the patients were from Kinondoni (40.28%) with relatively equal population sizes from the other two municipalities; Ilala and Temeke (28.8% and 30.8% respectively).

Table 1: Socio-demographic characteristics of HIV/AIDS patients with treatment failure attending Amtullabhai Karimjee Clinic

Variable	Total patients n = 246	Percentage %
Sex: Female Male	154 92	62.6% 37.4%
Age group (years): 19-32 33-46 47+	51 129 66	20.7% 52.4% 26.8%
Occupation: Employed	174	70.7%

Unemployed	54	22.0%
Student	8	3.3%
Self employed	10	4.1%
Marital status:		
Cohabiting	7	2.8%
Divorced	36	14.6%
Married	90	36.6%
Single	70	28.5%
widowed	43	17.5%
Municipality:		
Ilala	76	30.8%
Kinondoni	99	40.3%
Temeke	71	28.8%

The prevalence of mucocutaneous disorders among the study population was 52.8% (130/246). There was a striking female preponderance; the proportion affected by mucocutaneous disorders of [61.0% (94/154)] was almost one and a half times that of males [39.1% (36/92)]. This difference was statistically significant (p=0.0009).

Another finding observed among the 4 age groups studied was as follows. The proportion of patients affected with mucocutaneous disorders in the age group 19-32 years was 32/51 (62.7%). In contrast, in those above 47 years fewer patients were affected 27/66 (40.9%). This difference was not statistically significant (p=0.05). Regarding occupation, of patients affected with mucocutaneous disorders higher percent of the disorders was seen in students 5/8(62.5%) as compared to other types of occupations, but this difference was not statistically significant (p=0.7). Single patients appeared to be affected more 46/70 (65.7%) when compared with other forms of marital status, the difference is not statistically significant (p=0.1)

Table 2: Mucocutaneous disorders by Socio-demographic characteristics

Variable(n)	Patients with mucocutaneous disorders n=130 (52.8%)	Patients without mucocutaneous disorder n=116 (47.2%)	P value
Sex:			
Female	94 (61.0%)	60 (39.0%)	
Male	36 (39.1%)	56 (60.9%)	0.0009
Age group:			
19 - 32	32(62.7%)	19 (37.3%)	0.05
33-46	71 (55.0%)	58 (45.0%)	
>47	27 (40.9%)	39 (59.1%)	
Occupation:			
Employed	93 (53.4%)	81(46.6%)	0.7
Unemployed	28 (51.9%)	26 (48.1%)	
Student	5 (62.5%)	3 (37.5%)	
Self employed	4 (40.0%)	6 (60%)	
Marital status:			
Cohabiting	3 (42.9%)	4 (57.1/%)	0.1
Divorced	18 (50%)	18 (50%)	
Married	40 (44.4%)	50 (55.6%)	
Single	46 (65.7%)	24 (34.3 %)	
Widowed	23 (53.5%)	20 (46.5%)	

The frequency of mucocutaneous disorders grouped by dermatological categories is summarized in table 3. Inflammatory/ papulosquamous disorders ranked highest in prevalence with a total of 79/130 (60.8%) of the 130, pruritic papular eruption was the most common comprising 54.6% (71/130); seborrhoeic dermatitis and eczema had an equal proportion of

patients affected which was 2.3% (3/130). Lichenoid hypersensitivity reaction and lichen simplex chronicus ranked lowest, each with 1 patient.

Infectious diseases followed with a prevalence of 41.3% (61/130). Of these, fungal infections were most predominant (31/130, 23.8%) closely followed by viral infections 23.0%, 30/130). Malignancies were encountered in 3 patients; two had Kaposi's sarcoma while one had squamous cell carcinoma.

Xerosis and Acne were the most common miscellaneous disorders each with a prevalence of 3/130 (2.3%).

Table 3: Distribution of mucocutaneous disorders by various dermatologic categories among HIV/AIDS treatment failure patients attending Amtulabhai Karimjee clinic n=130

Dermatological conditions	Number	Percentage of n
I: Inflammatory/ Papulosquamous:		
PPE	71	54.6
Seborrhoeic dermatitis	3	2.3
Eczema	3	2.3
Lichenoid hypersensistivity reaction	1	1
Lichen simplex chronicus	1	1
Total	**79**	**60.8**
II: Infectious conditions:	**64**	**49.2**
Fungal infections	**31**	**23.8**
Dermatophytes	**17**	**13.1**
Tinea corporis	6	4.6
Onychomycosis	3	2.3
Tinea pedis	6	4.6

Tinea capitis	2	1.5
Yeasts	**14**	**10.8**
Pityriasis versicolor	8	6.2
Oral candidiasis	1	1
Vaginal candidiasis	2	1.5
Intertrigo	3	2.3
Bacterial infections	**3**	**2.3**
Abscess	2	1.5
Folliculitis	1	1
Viral infections	**30**	**20.8**
Herpes zoster	6	4.6
Molluscum contagiosum	3	2.3
Condyloma acuminatum	7	5.4
Herpes simplex	7	5.4
Verruca plana	6	4.6
Anal wart	1	1
III. Infestations	**2**	**1.53**
Scabies	2	1.53
IV. Miscellaneous/Others	**12**	**9.2**
Xerosis	3	2.3
Acne	3	2.3
Angular stomatitis	2	1.5
Pruritus	1	1
Alopecia	1	1
Photosensitive dermatitis	2	1.5
V. Malignancies	**3**	**2.30**
Kaposi sarcoma	2	1.5
Squamous cell carcinoma	1	1

NB: Some patients had more than one diagnosis

Among the 130 patients with mucocutaneous disorders, 80.8% had one type of skin disorder and 19.2% had 2 or more types of skin disorders. This is shown in table 4.

Table 4: Frequency of types of skin disorders in HIV treatment failure patients

Number of types of skin disorder	Frequency	%
1 type of disorder	105	80.8%
2 types of disorders	20	16.1%
3 types of disorders	5	3.1%
Total	**130**	**100%**

Table 5: Frequency of the most common mucocutaneous disorders according to sex

Disease	Females	Males	P value
PPE	54 (76.1%)	17 (23.9%)	0.000
Tinea corporis	4 (66.7%)	2 (33.3%)	NS
Condyloma acuminate	6 (85.7%)	1(14.3%)	NS
Herpes simplex	5 (100%)	-	0.07
Pityriasis vesicolor	3 (37.5%)	5 (62.5%)	NS
Verruca plana	3 (75%)	1 (25%)	NS
Tinea pedis	5 (83.3%)	1 (16.7%)	NS
Onychomycosis	3 (50%)	3 (50%)	NS
Herpes zoster	3 (50%)	3 (50%)	NS
Xerosis	3 (100%)	-	0.2

Table 5 shows that the prevalence of PPE in females of 76.1% (54/71) was three times that of males 13% (17/71) and the difference was statistically significant (p =0.000), whereas herpes simplex 100% (5/5) and xerosis 100% (3/3) were only seen in females. A total of 6 females presented with condyloma acuminata whereas for their male counterparts only 1 patient had condyloma acuminata .

Out Of 130 treatment failure patients with mucocutaneous disorder , 90/130 (69.2%) had CD4^{+} -T cell counts of less than 200 cells/µl, while the remaining 40/130(30.8%) had CD4^{+} -T cell counts greater than 200 cells/µl. Of those with CD4^{+} -T cell counts less 200 cells/µl, PPE was encountered more frequently 53/90 (58.8%) than other mucocutaneous disorders, and this was statistically significant (p=0.003).

The mean and median CD4^{+} -T cell counts of patients with ART treatment failure having the most frequent mucocutaneous disorders are presented in table 6. Patients with PPE which appeared frequently, had a mean CD4^{+} -T cell counts of 166.1 cells/µl and median of 87 cells/µl.

Table 6: Mean and median CD4^{+} -T cell counts of patients with ART treatment failure having the most frequent mucocutaneous disorders

Disease	Mean CD4 count (cells/µl)	Median CD4 count	95% CI
PPE	166.1	92	87.4-246.5
Tinea corporis	149.8	78	85.3-214.3
Condyloma accuminata	171	83	48.0-293.1
Herpes simplex	132.4	67	46-271
Pityriasis vesicolor	137.3	101	70.9-203.8
Verruca plana	91	59	27-210

7.0 DISCUSSION

This study aimed at describing the pattern of mucocutaneous disorders among HIV/AIDS adult patients with anti-retroviral treatment failure. Female were most prevalent and majority of them presented with mucocutaneous disorders where by PPE were the most frequent mucocutaneous disorders.

In this study out of the 246 ART treatment failure patients who participated, about one-third (37.2%) were males, showing a female preponderance of 62.8% .The findings of Raphael et al.[29] from Nigeria who reported a female predominance of 67% are consistent with this study. This higher frequency in females could probably be attributed to the large number of females affected by HIV/AIDS in the respective study populations. Furthermore, it is well documented that attendance to CTC's for initiation as well as follow up of ARV's is greater in females (NACP report 2009).[30] who would therefore be picked up early, as soon as they develop treatment failure than their male counterparts.

Moreover, in this study female subjects dominated the study population presenting with the majority of mucocutaneous manifestations of which inflammatory conditions were most prevalent. Reasons as to what caused females to be mostly affected are not clearly known since there is scanty literature in this area. Hypothesis which could attribute to this observation could be that most females apply cosmetic preparations which may act as triggers for skin reactions or due to the fact that, in most CTCs females attend more frequently as compared to males.

Most of the patients in this study were in the age groups of 19-32 and 33-46 years and this could be explained by the fact that this is the age group which is most sexually active and consequently more likely to be HIV infected.

Mucocutaneous disorders were observed in 52.8% subjects with treatment failure. The inflammatory, non-infective disorders accounted for the highest frequency (60.8%) followed by infective dermatoses like fungal and viral infections. Many other studies have documented similar findings; however, none of them focused on patients with ARV treatment failure. Most researchers report on mucocutaneous dermatoses among HIV/AIDS patients in general who may not have treatment failure. Thompson et al from Jamaica observed a similar order of frequency of mucocutaneous disorders; inflammatory disorders accounting for 41% followed by 28% and 18% in the fungal and viral infection groups respectively among HIV/AIDS patients who were not treatment failure cases. Farrokh et al from Sanandaj city, Iran.[31] however, reported contrasting results the highest frequency being that of fungal infections, 55.7%. The possible reason for a higher frequency of inflammatory disorders in our study could be the strikingly high proportion of PPE among these patients (44.2%). Pruritic papular eruption of HIV/AIDS has been described as being very common among HIV/AIDS patients particularly in tropical as well as subtropical areas and in individuals of African descent. Several authors have concluded that PPE of HIV/AIDS remains the most common inflammatory mucocutaneous disorder (Thompson et al from Kingston, Jamaica, 32%.[32]; Goldstone et al in Miami Florida, 11.4%.[33] and Pitche et al in Togo, 33.3%)[34]. This study has also shown that PPE of HIV/AIDS is still common even among patients with ARV treatment failure.

Because of immunosuppression, HIV-positive patients with treatment failure have multiple cutaneous lesions, which may be inflammatory, infectious, or neoplastic in nature. In our study, multiple lesions were observed in 44 of 130 (33.9%) patients, which is similar to the findings of Jindal et al from India. [35] Generally, the spectrum of mucocutaneous disorders in HIV/AIDS adult patients with ARV treatment failure as demonstrated in our study did not show a striking difference from that commonly reported in ARV naïve patients.

In this study patients with $CD4^+$ -T cell counts less than 200 cells/µl had an increased prevalence of PPE than other mucocutaneous disorders. These findings are similar to Pedro et

al.[36]who stated that patients with $CD4^+$ -T cell counts less than 200 cells/µl had an increased prevalence of folliculitis and prurigo nodularis in Patients not receiving HAART.

Also from this study we found out the mean $CD4^+$ -T cell counts among patients with PPE to be 166.1cells/µl, which is almost similar to the finding of vamseedhar et al.[37] from India who did a study on Histopathological features of pruritic papular eruptions in HIV-infected patients in relationship with CD4, CD8 counts. They found out the mean $CD4^+$ -T cell counts for PPE to be 186.49cells/mm^{3}.

8.0 CONCLUSIONS:

 – Majority of patients with treatment failure were females
 – Mucocutaneous disorders were a common presentation in patients on treatment failure
 – Chronic persistent PPE was the most frequent mucocutaneous disorder finding
 – More than two third of the mucocutaneous disorders presented at the CD4 T cell counts less than 200 cells/µl

9.0 LIMITATIONS:

Although the (study) sample size was adequate for this study as AKC is a treatment failure centre receiving patients from 29 sites, this population was not sufficient to produce representative findings for Dar es Salaam as several sites were not included.

10.0 RECOMMENDATIONS:

Since there is a high frequency of mucocutaneous disorders in patients with ART treatment failure clinicians should be sensitized to perform a thorough dermatological examination in each patient. In order to this these patients should be undressed to look for skin lesions.

PPE is marker of HIV infection and continues to be the most common mucocutaneous disorder even among patients with treatment failure. Persistent PPE should increase the index of suspicion of ARV failure

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12.0 APPENDIX A – QUESTIONNAIRE

Part I: Demographic data

1. ID NO …………………….

2. Age ………………………

3. Sex

     a) Male ☐

     b) Female ☐

4. District …………………….

5. Region………………………

6. Occupation……………………..

7. Marital status

     a) Single   b) Married   c) Cohabiting

     d) Divorced   e) Widowed   f) Separated

Part II: Interview

8. When were you first diagnosed with HIV/AIDS?

     (a) <6 months ago

     (b) 6 months – 2 years

     (c) 2 – 5 years

     (d) 5+ years

9. Are you on ARVs?

     (a) Yes

     (b) No

10. IF Yes, When did you start ARV treatment?   …………..

11. What was the indicator for starting ARVs? ………………..

    (a) CD4 <200

    (b) Aids defining characteristics

    (c) Stage 3 CD4 <350, TB +ve/ other

12. What ARV combination are you on?

    (a) ………………………………..

    (b) ………………………………..

    (c) ………………………………..

    (d) ………………………………..

13. When were you diagnosed with treatment failure………..

14. What ARV combination are you on ……………………..

15. Do you have any skin disease/s at the moment?

    a.   Yes

    b.   No

    IF the answer is No, skip to question 18

16. When did you first realize you had a skin disease?

    (a) Before starting ARV

    (b) After starting 1st line

    (b) After starting 2nd line

17. Have you noticed any change/changes in your skin disorder/s?

    (a) Yes

    (b) No

      IF the answer is yes go to question 17

18. What has happened to your skin disease?

(a) Worsened   (c) Improved

(b) Remained the same   (d) Disappeared

19. Have you ever suffered from any skin disease since diagnosed with treatment failure?

    (a) Yes

    (b) No

20. If yes describe…………………
            Inferred diagnosis………………..

 21 Have you received any medication for your skin disease other than ARVS?

    (a) Yes

    (b) No

22. If yes what treatment?

                    i. Steroids
                   ii. Antifungal
                  iii. Cytotoxics
                   iv. Others
                    v. Can't tell

23. Has your ARV regimen been changed at any point?

    (a) Yes

    (b) No

24. How many times has it been changed?

    (a) Once

    (b) Twice

    (c) Thrice

25. Why was it changed?

(a) Side effects

(b) Treatment failure

(c) TB treatment

26. From which ARV combination was it changed.

(a) ……………………………….

(b) ……………………………….

(c) ……………………………….

Part II: Dermatological examination

27. (a) Type/s of lesion/s

(b) Distribution

28. Diagnosis ………..

Part III: Laboratory investigations

29.   CD$_4$ cell count values

(a) Current………

30. Results obtained

i) Biopsy for Histology/Cytology…………….

ii) skin/Nail scraping for KOH

31. Culture growth (i) Yes (ii) No

i)Pus Swab/aspirates for bacterial

13.0 APPENDIX B – INFORMED CONSENT FORM (ENGLISH VERSION)

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

DIRECTORATE OF RESEARCH AND PUBLICATIONS, MUHAS

INFORMED CONSENT FORM

ID-NO………….

Consent to Participate in a Study

Greetings! My name is **Dr. Pamela F. Kaaya ,** I am working on a research with the objective of To determine the pattern of mucocutaneous disorders among HIV/AIDS patients with treatment failure attending Amtulabhai Karimjee Treatment failure Clinic (AKC) in Dar es Salaam.

Purpose of the study

The study is conducted in partial fulfillment of the requirements for the degree of Master of Medicine in Internal Medicine with the aim of learning more about the pattern of mucocutaneous disorders among HIV/AIDS patients with treatment failure attending Amtulabai Karimjee Treatment failure clinic (AKC) in Dar es Salaam.

You have been randomly selected as a possible participant in this study because you reside in this area. You will be one among 246 patients attending AKC treatment failure clinic in Dar es Salaam.

What Participation Involves

Should you agree to participate, you will be asked some questions concerning any skin problems you have or have had in the past and how they have evolved. You will be required to submit a blood sample for a complete blood count as well as CD4 cell count. Some of you may be asked to undergo other investigations like skin biopsies for histology, swabs and/or scrapings for bacteriological and/or mycological identification, culture and sensitivity testing.

Confidentiality

I assure you that any information obtained in connection with you in this study and that can be identified with you will remain confidential and the final report will be sent to the Muhimbili University of Health and Allied Sciences without disclosing your identity. To achieve this, your name will not be written on any questionnaire or in any report/documents that might allow someone to identify you. Your name will not be linked with the research information in any way. All information collected on forms will be entered into computers with only the study identification number. Confidentiality will be observed and unauthorized persons will have no access to the data collected.

Risks

Despite pain that you might experience during drawing of blood or tissue sampling via biopsies, effects of local anesthesia and inconveniences in your time, there are no other risks to being in this study.

Right to withdraw from the study and Alternatives

Taking part in this study is completely voluntary. You can decide to withdraw your participation at any time, even if you have already given in your consent. Refusal to participate or withdrawal from the study will not involve penalty.

Benefits

We hope that the results obtained from this study will provide a useful tool to assist in the clinical diagnosis and management of HIV/AIDS patients with treatment failure.

Who to Contact

If you have questions about this study please contact the **Principal Investigator**, **Dr Pamela F. Kaaya** of Muhimbili University of Health and Allied Sciences, P. O. Box 65001, Dar es Salaam.

If you have questions about your rights as a participant, you may call Prof. E. F. Lyamuya, Chairperson of the Senate Research and Publications Committee, P. O. Box 65001, Telephone : 255 22 2152489 Dar es Salaam and **Dr. Y. Mgonda** who is the supervisor of this study (Tel. 0754 277 554)

.

Signature:

Do you agree?

Participant agrees ………………….. Participant does NOT agree………………….

I ……………………………………. have read the contents in this form. My questions have been answered. I agree to participate in this study.

Signature of participant ....

Signature of PI or designee…………………………….

Date of signed consent ………………………………….

14.0 APPENDIX C – INFORMED CONSENT FORM (SWAHILI VERSION)

CHUO KIKUU CHA SAYANSI ZA AFYA MUHIMBILI

KURUGENZI YA TAFITI NA UCHAPISHAJI

FOMU YA RIDHAA

Namba ya utambulisho……….

Ridhaa ya kushiriki kwenye utafitiisha

Hujambo! Ninaitwa **Dr. Pamela F. Kaaya ,** nashughulika kwenye utafiti wenye lengo la **kutathimini magonjwa ya ngozi kwa wagonjwa wa VVU ambao dawa za kurefusha maisha (yaani ARV) zimeshindwa kuonyesha matokeo mazuri**

Madhumuni ya Utafiti

Utafiti huu unafanyika kama sehemu ya shahada ya uzamili ya tiba ya Chuo Kikuu cha Afya na Sayansi ya Tiba Muhimbili. Utafiti unalenga kuchunguza magonjwa ya ngozi kwa wagonjwa wa VVU ambao tiba imeshindwa kupambana na ukimwi. Tafadhali kuwa mkweli na muwazi kwa vile matokeo ya utafiti huu yanaweza yakatoa maamuzi na mapendekezo ya baadaye.

Nini kinahitajika ili kushiriki

Kama umeamua kushiriki, nitakuuliza maswali kuhusu tatizo lolote la ngozi ulilonalo au ulilowahi kupata. Tutakutoa damu mara moja kiasi cha mililita 7(sawa na kijiko kimoja na nusu) na tutaitumia kupima wingi wa damu pamoja na kiwango chako cha kinga mwilini (yaani CD4).Vile vile unaweza kuchukuliwa vipimo vya ngozi kwa ajili ya uchunguzi zaidi.

Usiri wa taarifa

Taarifa zozote zile zitakazopatikana katika utafiti huu ambazo zinaweza zikakutambulisha wewe zitabaki kuwa siri, taarifa ya mwisho ya utafiti huu itapelekwa chuo kikuu cha Muhimbili pasipo kutambulisha taarifa zako binafsi.

Athari za kushiriki

Athari unazoweza kupata ni maumivu madogo wakati unapotolewa vipimo kamavikihitajika kwa mfano kutoa kinyama cha ngozi kwaajili ya kukipima zaidi ya hayo hakuna athari nyingine zozote za kushiriki katika utafiti huu.

Haki ya kujitoa au vinginevyo

Ushiriki katika utafiti huu ni wa hiari. Unaweza kuacha kushiriki katika utafiti huu muda wowote hata kama ulikwishatoa idhini yako. Kukataa kushiriki au kujitoa kutoka kwenye utafiti huu hakutahusisha adhabu yoyote.

Faida

Matokeo ya utafiti huu yataweza kutusaidia kuwa na ufahamu wa kutosha kwa magonjwa ya ngozi kwa wagonjwa wa VVU ambao dawa za kurefusha maisha (yaani ARV) zimeshindwa kuonyesha matokeo mazuri.

Madhara

Hutegemewi kupata madhara yoyote kutokana na ushiriki wako katika utafiti huu.

Nani wa kuwasiliana naye

Kama una maswali kuhusiana na utafiti huu, wasiliana na Mtafiti mkuu wa utafiti huu, **Dr Pamela F. Kaaya** wa Chuo Kikuu cha Afya na Sayansi ya Tiba Muhimbili, S. L. P. 65001, Dar es Salaam.

Kama una swali kuhusu haki zako kama mshiriki unaweza kumpigia simu **Prof. E. F. Lyamuya**, Mwenyekiti wa kamati ya Utafiti na Uchapishaji, S.L.P 65001, Simu: 255 22 2152489 Dar es Salaam au msimamizi wa utafiti huu **Dr Y. Mgonda** (0754 277 554).

Sahihi:

Je umekubali?

Mshiriki amekubali ……........................... Mshiriki hajakubali………................

Mimi .... nimesoma maelezo ya fomu hii.

Maswali yangu yamejibiwa.Nakubali kushiriki katika utafiti huu.

Sahihi ya mshiriki…………………………………………………

Sahihi ya mtafiti mkuu au mwakilishi…………………………………………

Tarehe ya kutia sahihi ya idhini ya kushiriki………………………..