FACTORS ASSOCIATED WITH HIV TREATMENT FAILURE.

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DECLARATION

I certify that this dissertation is my original work and has not been presented for a degree in any other university.

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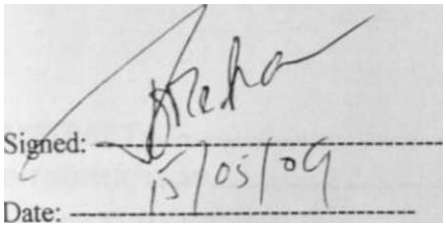

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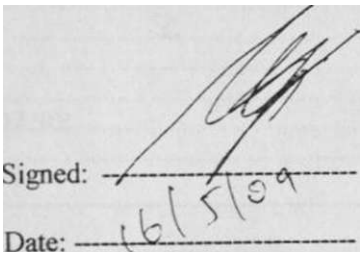

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ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
AMPATH	Academic Model for Prevention and Treatment of HIV.
ART	Antiretroviral Therapy
ARV	Anti retroviral
AZT	Zidovudine
CYP450	Cytochrome P 450
d4T	Stavudine
DDI	Didanosine
DNA	Deoxy -ribonucleic acid
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immune Deficiency Virus
HR	Hazard Ratio
INH	Isoniazid
IRIS	Immune Reconstitution Inflammatory Syndrome
KAIS	Kenya AIDS Indicator Survey
Lp/Rt	Ritonavir boosted Lopinavir
MRS	Medical Record System
NASCOP	National Aids and STI Control Program
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
O.I	Opportunistic infections
OR	Odds ratio
PEPFAR	Presidents Emergency Plan for AIDS Relief.
PI	Protease Inhibitors
PMTCT	Prevention of Mother to Child Transmission

RNA	Ribonucleic acid
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
UNAIDS	UNITED NATIONS PROGRAMME ON HIV/AIDS
WHO	World Health Organization

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1.0 ABSTRACT

Background: The availability of HAART has had a profound positive effect on HIV morbidity and mortality. However, the occurrence of primary treatment failure is a drawback to this success resulting in higher cost of treatment and poor outcomes. It is therefore important to establish the factors that are associated with primary HIV treatment failure. These factors can be used to identify patients at high risk of early treatment failure, and to screen for treatment failure resulting in earlier diagnosis.

Objectives: To determine the factors associated with HIV treatment failure.

Design: Nested case control study

Subjects: Adult HIV patients in 18 HIV clinics run by AMPATH in Western Kenya.

Methods: All previously, treatment naive patients started on HAART and subsequently diagnosed to have treatment failure between Feb 2006 and August 2008, formed the study cases. The control group was made up of; previously treatment naive patients started on HAART at similar time to the cases and who had sustained immunologic response. Data on demographic, clinical characteristics and laboratory parameters was extracted from the AMPATH medical records database. The data was then analyzed.

Results: Data on 12027 patients was analyzed, with 5709 in the cases and 6314 in the controls. Factors that were associated with increased risk of immunologic failure were age above 45 **(O.R 1.21),** male gender **(O.R 1.22)** and urban residence **(O.R 1.09).**Perfect adherence and first line effavirenz based regimen were protective

Conclusion: Poor adherence, male gender, age above 45yrs and living in an urban area, are risk factors for immunologic treatment failure.

2.0 INTRODUCTION

Infection with Human immunodeficiency virus (HIV) results in progressive destruction of the host immune system resulting in a state of immune deficiency and hence opportunistic infections. Antiretroviral (ARV) therapy is aimed at reducing viral replication resulting in reduction of viral loads and consequently allowing the immunity to reconstitute. Persistence of viral replication, immune depletion and clinical deterioration beyond set limits despite ARV therapy, is referred to as treatment failure.

Causes of ARV treatment failure include drug resistances, poor adherence to treatment, and. variations in drug pharmacokinetics. Several factors influence development of treatment failure through their effect on these causes. These factors include patient factors, therapeutic factors and co morbidities. The association of these factors with treatment failure so far has been variable depending on the community under study and study methodology. Identifying the specific associations that are relevant, especially in our set up where ARV programs are still being rolled out in numbers is crucial in establishing measures that will combat them early and hence prolong duration of first line therapy.

3.0 LITERATURE REVIEW

3.1 EPIDEMIOLOGY

3.11 Global statistics

The current global HIV prevalence seems to have stabilised though the number of people living with HIV is increasing due to increased survival time with the use of ARVs. New infections are still rampant with 2.5 million infections reported in 2007 alone. This translates to 6800 new infections daily. Mortality from HIV is also still high with 2.1 million deaths reported in the same year equating to 5700 deaths daily. The implications of this in terms of economic and human resources, number of orphans and governance structures is massive [1].

Although there has been an over 7 fold increase in the number of HIV patients on treatment in a 4yr period , only 31% of the worlds population in need have been reached. The continued transmission leading to increasing numbers of those in need of treatment, combined with occurrence of treatment failure, makes control of this disease extremely challenging.

3.12 SUB-SAHARAN AFRICA.

Though Sub-Saharan Africa has just 11% of the world's population, it carries 68% of the adult, and 90 % of the childhood HIV infections, which translates to 22.5 million people living with HIV in the region [1,2]. Women are much more affected than men in this region contributing 61% of the total number of adults infected. This is partly because of a mostly heterosexual transmission.

76% of the global HIV related mortality in 2007, occurred in sub-Saharan Africa. This reflects the fact that despite a 10 fold increase in ARV use in the region from 2003-2006, only 28% of the 4.8 million HIV patients who require treatment had accessed it by December 2006 [3], As a result, life expectancy in the region has declined to below 50 years. The need for sound ARV programs which ensure minimal occurrence of treatment failure, given the little resources available in the region, can therefore not be overemphasised.

3.13 KENYA

The prevalence of HIV in Kenya peaked in the late 1990s at 10% [3], In 2004 the prevalence had already declined to 6.1%, and by end of 2006 it was reported to be 5.1%.

Recent data released from a survey by World Health Organization (WHO), Centre for Disease Control (CDC) and Kenya Medical Research Institute (KEMRI), referred to as Kenya AIDS indicator Survey (KAIS) and carried out in 2007, showed a rising prevalence of 7.8%. It also showed that only a third of the country's population has been tested and 4 out of 5 infected people were unaware of their status [4], This means that the risk of late diagnosis and hence late onset of therapy is still high.

Currently there is little data on prevalence of treatment failure in Kenya. Wools Kaloustian et al reported 11.9 % treatment failure in a Western Kenyan cohort of 2059 patients with a mean time to treatment failure of 3 years [5], Hawkins et al also reported a 14% rate of treatment failure in an urban cohort in Nairobi [6].

3.2 HIV TREATMENT

The discovery of the first class of antiretroviral drugs was heralded by the realisation that the enzyme reverse transcriptase was central to HIV replication. This led to a search for agents that would inhibit this enzyme with the first drug zidovudine (AZT) being discovered by Dr. Robert Y et al in 1985 [7], However, the benefits from AZT monotherapy were short-lived with rapid onset of resistance. In 1991 the second nucleoside reverse transcriptase inhibitor, didanosine (ddl) was approved and the practice of dual therapy combining AZT and ddl showed better results though still short-lived due to resistance.

The Highly Active Antiretroviral Therapy (HAART) era came with the advent of protease inhibitors in 1995-1996. HAART has so far shown the best response with massive decline in mortality and extension of life on average by 13yrs per individual [8]. Despite this progress, drug toxicity, continued spread of HIV and inability to offer cure compounded by resistance to treatment have continued to be major challenges. As a result, research continues in search of a better solution. More classes of drugs are now in use including fusion inhibitors, intergrase inhibitors and binding inhibitors but none is perfect.

3.21 ANTI RETROVIRAL THERAPY IN KENYA

ARV therapy in Kenya was first started in the private sector for those who could afford. Nucleoside analogue Reverse Transcriptase Inhibitors (NRTIs) were the first drugs commercially available in the late 1980s followed by Protease Inhibitors (Pis) in 1997, and Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) in 1999 [9].

Public sector provision of ARVs began on a pilot basis in five sites of the country in 2001. With time, this was scaled up with the help of donor funding, and by November 2005. 55000 people were receiving ARVs across the country.

As of September 2007, the number had more than doubled to 166,400 people on treatment [10].

The National AIDS and STI Control Program (NASCOP) operating under the Ministry of Medical Services, co-ordinates the roll-out of ARV programs for the ministry. It also formulated and updates the HIV treatment guidelines for the country [11].

Other providers of ARV treatment in the country include Faith-based organizations and hospitals, Non-governmental Organizations, Private (for-profit) hospitals, and Academic based organizations such as the Moi University- Indiana University collaborative organization in Western Kenya Academic Model for Prevention and Treatment of HIV (AMPATH).

Treatment guidelines used in Kenya are based on the WHO guidelines. They recommend the use of combinations of three drugs drawn from at least two classes out of the available. Protease inhibitors are often saved for second line treatment and hence recommended first line therapy consists of two NRTIs and one NNRTI. Specific recommendations as to what to start with in different circumstances and what to change to in case of toxicity and/or treatment failure are also given. Recommendations on monitoring of patients for adherence, toxicity and treatment failure are clearly provided [11]. Treatment efficacy is monitored clinically, and through CD4 counts at specified intervals. Because viral loads measurements are not widely available or affordable to most people, the guidelines prescribe their use only where there is suspected poor adherence, or where clinical response is good but CD4 response remains poor [11].

According to data from NASCOP headquarters in Nairobi, 400.000 people in Kenya required ARV by end of 2007, of which 213,000 were receiving treatment and 5000 were on second line therapy having failed the first line [12].

3.3 TREATMENT FAILURE

3.31 DEFINITION

Treatment failure is defined in terms of clinical disease progression, immunologic failure and/or virologic failure [11].

Diagnosis of ARV treatment failure is made based on. clinical criteria when the patient gets new or recurrent WHO stage 3 or 4 conditions after 6-12 months of ARV therapy despite optimizing adherence, treating opportunistic infections and excluding Immune Reconstitution Inflammatory Syndrome (IRIS). Developing these stage 3 or 4 conditions before completing 6 months of treatment may not necessarily signify failure as it could be due to pre-existing conditions or IRIS. Though monitoring clinical status of patients is important in detecting failure, it lacks specificity and sensitivity, and relying on it solely leads to delayed diagnosis or misdiagnosis.

Immunologic failure is defined as persistence of CD4 counts below lOOcells/mnr after 6 months of sustained antiretroviral therapy (ART) , or a persistent decline in CD4 counts to or below pre-therapy levels, or a 50% drop from on treatment peak value [11, 13].

The AMPATH project's definition of immunologic failure differs from the WHO one because it uses a >25% drop from peak CD4 achieved, rather than 50% drop. This was chosen based on work done by Hughes M.D. et al which documented an average within subject coefficient of variation for CD4 cell count of 25% among HIV patients in the USA implying that using 25% as the

cut off would have a higher sensitivity for detecting immunologic failure than 50% cut off [5,14].

The limitations of using immunologic parameters to diagnose treatment failure are that CD4 counts transiently drop during intercurrent infections, CD4 counts may fail to rise despite virologic response to treatment, and the exact peak CD4 count may be missed in between 2 measurements especially when taken 6 months apart as is the practice. In addition, CD4 drop lags behind virologic failure by several months resulting in delayed diagnosis of treatment failure and the attendant increased risk of Opportunistic Infections (O.I.) and death. Because of these limitations of immunologic parameters, the AMPATH project started doing viral loads on all patients found to have immunologic failure in February 2006.

A study done by Moore M.D. et al. found that defining treatment failure using failure of CD4 counts to rise at six and 12 months, had a sensitivity of 34% and 35%, and specificity of 94% and 95% respectively. From this study, the positive predictive value of the CD4 counts at 6 and 12 months was 75% and 79% and negative predictive value of 71% and 73% respectively. This showed that this definition used alone would cause misclassification of many patients [15]. In most resource poor settings however, combination of clinical and immunologic failure is still the only available and hence useful definition though not ideal.

Virologic failure is failure to reduce viral loads to undetectable levels or to less than 0.5 log $|_0$ after 24 weeks of ARV therapy, or sustained increase in viral loads after a period of full suppression^ 1,13]. Viral loads are the most ideal measure of treatment failure, but are unfortunately expensive and out of reach for most people. As a result, most programs use clinical and immunologic measures of failure.

3.32 CAUSES OF TREATMENT FAILURE

ARV treatment failure results from poor adherence, variability in drug pharmacokinetics and emergence of drug resistance. Most other factors that influence treatment failure do so through their effect on these three causes of failure.

3.321 Poor Adherence.

Poor adherence leads to oscillating drug levels and hence varying viral suppression at different times. This creates a perfect environment for selection for resistant mutants. In some instances, poor adherence results in circulating drug levels that are so low that the effect on viral replication is insignificant resulting in treatment failure even without drug resistance developing.

Adherence may be measured using different methods. The commonest measure employed is self-reported adherence and has been validated in several studies against response to therapy. In a meta-analysis, self reported adherence was found to be positively associated with virologic response to HAART. The association was strongest during the primary ARV regimen, probably due to higher likelihood of attaining complete virologic suppression, and of patients self reporting adherence earlier on in treatment [16]. Another mode of self reported adherence is the use of pharmacy refill claim forms. Bisson G .P. et al compared use of pharmacy refill adherence assessment to CD4 count changes for predicting virologic failure and found that adherence levels outperformed CD4 counts in predicting current virologic failure. Adherence assessment was as predictive as changes in CD4 counts from onset of treatment to time of failure and predicted virologic failure 3 months before it occurred. Use of pharmacy refill adherence was possible in Bisson's study because it was done in patients in private care who had to fill claim forms every time they got a refill, which is not the case in the public setup. Nevertheless, this study brought

out the importance of non-adherence as a causative and predictor of treatment failure [17].

Other measures of adherence testing include pill counts, which is more objective but more time consuming. The most objective method is measuring serum drug levels, but it is expensive and not widely available. Adherence testing is so useful in monitoring treatment that all clinical guidelines recommend it as a central component of HIV care.

Levels of adherence that results in treatment failure vary from drug to drug as was demonstrated by Maggiolo F et al in their study on effects of adherence on virologic outcomes [18], This may explain why some studies may have found no relationship of adherence and treatment failure.

Whereas very poor adherence rapidly leads to treatment failure due to complete lack of viral suppression, high levels of adherence in patients with incomplete viral suppression has been associated with rapid development of highly resistant virus. This may be due to the prolonged high adherence coupled with incomplete viral suppression resulting in increased selection pressure for resistant virus as was demonstrated by Bangsberg et al. in 2003 [19].

3.322. Drug Resistance.

Drug resistance results from emergence of mutations in proteins that are targeted by a particular ARV agent. When it occurs prior to exposure to ARVs it is referred to as primary resistance, and may be due to infection with an already resistant virus, or it may occur de novo as a result of random mutations especially in patients with extremely high viral loads [20]. Secondary drug resistance on the other hand, occurs in patients on treatment but with suboptimal suppression of viral replication, which results in mutations, some of which confer survival advantage in the presence of the drugs. Continued

exposure to these same drugs ensures clearance of the sensitive virus while the resistant virus continues to replicate and forms the new pool of virus with time. This new pool of virus builds up the viral load, and leads to worsening immunologic and clinical status of the patient.

During the pre-HAART era. drug resistance occurred more rapidly due to suboptimal suppression of viral replication and. fewer mutations were required to confer resistance, since only one or 2 drugs were used at a time.

With the advent of HAART, occurrence of resistance was slowed down by the almost complete suppression of viral replication and a decline in prevalence of resistance to NRTIS, Pis and NNRTIs has been documented [21].

3.323. ARVs Pharmacokinetic Variability

Differences in ARV drug absorption, cellular activation, distribution and clearance results in varying blood levels of active drug. Where the result is suboptimal levels of active drug, resistance and treatment failure develop. On the other hand increased blood levels of particular drugs may cause increased toxicity and resultant poor adherence or discontinuation of treatment.

Drug Absorption.

Poor absorption of ARVs may occur due to presence of gastrointestinal diseases common in HIV infection, or interactions with food and/or drugs administered concurrently. These interactions such as interaction of ARVs with proton pump inhibitors, and with anti-infective agents, have been described in many studies [22,23]. In instances where hardly any absorption takes place, no suppression of viral replication occurs and early treatment failure without drug resistance results. In contrast, when partial absorption occurs, suboptimal drug levels achieved result in incomplete suppression of viral replication and resistance.

Drug activation.

Many NRTIs require phosphorylation in order to be activated. Individual variations in the phosphorylation mechanism have been described. In one study reported by Anderson P. L. et al, women and people with low baseline CD4 counts were reported to have higher AZT and lamivudine (3TC) triphosphate levels. In women these levels were 2.3 and 1.6 fold, respectively, higher than in men and they achieved HIV ribonucleic acid (RNA) levels <50copies/ml, twice as fast as men. Toxicities from NRTIs have been found to be commoner in women and people with low baseline CD4 counts because of the higher active blood drug levels, and this may affect adherence [24],

Drug Metabolism

Differences in rates of drug metabolism and hence drug clearance, affect circulating drug levels and outcomes of treatment. Some ARV drugs are metabolized through the cytochrome P450 system. This system is inhibited by certain drugs such as ritonavir, resulting in higher levels of other co-administered antiretroviral such as saquinavir and lopinavir. Because of this interaction, ritonavir is used to boost other Pis. Such interactions however may be harmful by resulting in increased toxicity.

Some drugs such as rifampicin are enzyme inducers increasing the rate of metabolism of most ARVs resulting in decreased drug levels and decreased drug efficacy [25]. Because of the importance of rifampicin in TB treatment, and the high prevalence of TB infection in HIV infected patients. TB treatment is a major cause of ARV switch especially from ncvirapine (NVP) to efavirenz (EFV), and may influence treatment outcome.

Results from the Aids Clinical Trial Group(ACTG) A5095 revealed a genetic polymorphism in the Cytochrome-P450 enzyme system, which is associated

with a slower clearance of effavirenz. This polymorphism was found to be more common in African Americans than Caucasians. Though this particular study did not find a direct correlation of genetic subtypes and adverse events or discontinuation rates, the higher drug levels found may affect adherence rates on the long term, by causing toxicity [26].

3.33. FACTORS INFLUENCING CAUSES OF TREATMENT FAILURE

3.331 Patient factors.

Gender

The debate on effect of gender on HIV treatment outcomes has continued for long with studies in different settings giving differing results. Women are unique because of the interplay of the female sex hormones with the immune system. In addition, differences in drug handling as alluded to earlier may affect treatment outcomes.

In one study done in Western Kenya, males were found to be more likely to be lost to follow up, have slower rise in CD4 counts and a tendency towards earlier progression to treatment failure than females[5]. A different study in an urban Kenyan clinic found male gender to be an independent predictor of regimen switch.[6] These results may be due to better treatment outcomes in females or existence of confounders such as differences in disease severity at initiation of treatment.

In a study done in Spain, women had significantly higher mean CD4 counts and a less likelihood of Acquired Immune Deficiency Syndrome (AIDS) defining condition at baseline than men. Despite this , there was no significant difference in time to treatment failure or death while on HAART[27]. Similar findings were documented in the Eurosida cohort with men having lower baseline CD4 counts but no difference in time to virologic and immunologic response, or to AIDS defining illness [28],

It is therefore not clear whether the gender discrepancy in ARV treatment outcomes is more in the African setting, or a result of differential utilization of the available therapeutic interventions.

Age

Older age has been associated with faster progression of HIV and shorter survival time after an AIDS diagnosis. Micheloud D et al described a statistically significant slower rise in CD4 counts for every 5-year increase in age. In addition, they found an overall poorer CD4 recovery for patients aged >45yrs compared to those <45yrs [29].

In an Italian study that ran on for 48 weeks, patients aged over 50yrs had similar virologic and immunologic response to HAART to a younger group of patients. The older group was nonetheless found to be significantly at higher risk for renal, metabolic and severe hepatic toxicities. They also were more likely to develop co-morbidities requiring treatment [30], It is possible that had the follow up been longer a difference in treatment outcomes would have been recorded.

The physiologic changes that occur with ageing which include increased risk of infection, reduced immune-competence and development of co-morbidities may explain the effects of age on HIV treatment outcomes.

Disclosure

Disclosure of HIV status to family members in a Tanzanian study was protective against virologic failure. In this study, other predictors were adherence and proportion of time on self-funded therapy [31]. It is possible that disclosure led to more financial support from family and hence better adherence and less treatment failure. The effect of disclosure on adherence and utilization of health services even when treatment is funded may still be significant enough to affect treatment outcomes.

Disease severity

CD4 cell counts, HIV viral loads and WHO clinical stage, define disease severity in HIV infection. Baseline levels of these markers have consistently been associated with treatment outcomes.

Patients initiating ARVs with advanced WHO stage are likely to be severely ill and as a result have compromised adherence due to intolerance to ARV regimen. This is supported by a study by Monforte et al, that demonstrated that clinical AIDS at baseline was predictive of treatment failure [32].

In these same patients with advanced disease, CD4 cell counts are usually low resulting in increased opportunistic infections and polypharmacy. This not only affects adherence but also results in multiple drug interactions and unpredictable circulating drug levels culminating in either increased drug toxicity, or development of drug resistance and eventually treatment failure. A retrospective analysis of HIV infected patients in a clinic in Massachusetts found CD4 cell counts <200 at baseline to be independently predictive of treatment failure (HR-1.90. 95% C.I.1.78-4.07) [33].

In Western Kenya. Wools-Kaloustin et al found CD4 counts <100 at baseline to be associated with a three fold increase in mortality. Though in their study the cause of death was not clear, it is possible that many of these deaths followed treatment failure [5].

High viral loads are associated with high viral replication rates and hence increased rates of mutations resulting in a higher risk of primary resistance. Secondary resistance may also develop faster once therapy is initiated, because of the adherence compromise and altered pharmacokinetics. In a retrospective analysis of a randomized double blind phase III trial by Powdery et al. baseline

and nadir viral loads were found to have the best predictive value in determining treatment response and response duration [34].

3.332 Therapeutic Factors

Choice of ARVregimen

The efficacy of different ARVs may differ in different communities due to variations in pharmacogenomics as has been described for effavirenz in African Americans [26].

In a study done in Uganda by Kamya M R et al. the sole independent predictor of virologic failure in adults was treatment with stavudine (d4T), 3TC and NVP verses AZT, 3TC & EFV (OR 2.59 95% CI 1.20-5.59). Resistance testing in this group revealed only 3TC and NNRTI mutations [35]. Since (d4T), 3TC and NVP is the most common primary regimen in our set up. it would be important to find out whether our outcomes are similar.

A Cochrane database review on efficacy of NVP based regimens compared to EFV based ones, revealed no statistically significant difference in efficacy, [36]. Differences in treatment outcomes may therefore be due to toxicities and pharmacogenetic differences.

Effect of drug toxicity

Drug toxicity has been described as one of the commonest cause of treatment interruptions in many studies [5,6]. Treatment interruptions promote emergence of drug resistance because of unopposed viral replication.

In addition, when toxicity is not adequately addressed, adherence is compromised leading to treatment failure.

A significant increase in the risk of opportunistic infections was described in patients who had changed treatment due to toxicities, and it is likely that the increase in opportunistic infections was a result of treatment failure [6],

3.333 Co-morbidities

Effect of Tuberculosis treatment

The interaction between Tuberculosis (TB) and HIV has been widely studied. However, the effect of TB and its treatment on ARV treatment success or failure is not clear. Drugs used for TB treatment, especially rifampicin interact with many ARVs and often necessitate change of particular drugs such as NVP to EFV, or in pregnancy to triple NRTIs, which may compromise regimen efficacy. In addition, the higher pill burden during TB treatment could cause poor adherence, affecting treatment outcomes.

In a study done by Rajasekaram et al in India, patients with history of previous TB treatment had a 1.6 greater hazard's ratio (H.R) of treatment failure than those without [37]. Adherence levels in the two groups was not controlled for, hence the exact causes of this increased risk were not elucidated.

Hematological Abnormalities

Anemia has persistently been described as an independent predictor of mortality in HIV infected patients. Results from the Eurosida study group strongly supported this [38].

Similar results were replicated in Tanzania where HIV infected patients on their primary HAART regimen, with severe anemia had an estimated 1-year survival of 55.2% compared to 3.7% in non anemic patients [39].

Negative change in hemoglobin levels, in the Indian study by Rajasekaran et al. was associated with a 3.2 significantly greater HR of treatment failure in comparison to a positive change. In the same study, another hematological parameter found to be predictive of treatment failure was negative change in absolute lymphocyte count [37],

Absolute neutrophil counts were also described as being predictive of treatment failure in a study done in Massachusetts by Robbins et al with a count <1000/mm3 increasing the HR by 2.90 (95% C.I, 1.26-6.69) [33].

Hematological parameters are affordable and accessible in most health facilities even in developing countries and would therefore be very useful in monitoring treatment outcomes if found to be consistently predictive.

4.0 JUSTIFICATION

The fact that HAART has had a dramatically positive impact on HIV care cannot be disputed. However immunologic treatment failure does occur, with a recorded prevalence of 14% and 11.9% in Nairobi and Western Kenya respectively [5,6].

This has a negative impact on outcomes of HIV therapy because 2nd line options are more expensive, less available and in many cases more toxic. In addition, morbidity and mortality outcomes of 2nd line therapy may not be as favourable as 1st line.

Elucidating the factors associated with treatment failure in our set up is therefore of utmost importance as these may be modifiable allowing for postponement of primary treatment failure setting in.

5.0 OBJECTIVES

5.1 MAIN OBJECTIVE

To establish factors associated with HIV Immunologic treatment failure in the AMPATH cohort.

5.2 SPECIFIC OBJECTIVES

1) To describe patient factors in terms of demographics, disease severity and disclosure in patients with immunologic treatment failure (cases) and those without immunologic treatment failure (controls).

2) To describe therapeutic factors in terms of choice of first line ART and toxicities, in cases and controls.

3) To describe the co morbidities experienced in particular tuberculosis and hematological abnormalities in cases and controls.

4) To determine the predictors of immunologic treatment failure from these factors.

6.0 METHODOLOGY

6.1 STUDY DESIGN

Nested case control study.

6.2 STUDY SETTING

This study was conducted at the Moi Teaching and Referral Hospital, AMPATH center.

AMPATH was initiated as a joint venture between Moi University, Moi Referral Hospital and Indiana University School of Medicine in 2001. Its initial goal was to establish a working model of both urban and rural comprehensive HIV preventive and treatment services and assess the barriers to and outcomes of antiviral therapy. Details of the development of this system are well described elsewhere. [40]

AMPATH conducts special ambulatory HIV clinics in both urban and rural sites in the western part of Kenya. Currently it runs clinics in 18 sites all running in the Ministry of Medical Services facilities. The main center is at the Moi Teaching & Referral Hospital, four centers are in District hospitals i.e. Webuye, Busia, Mt Elgon and Teso districts, and the rest in health centers.

Some of these centers have satellite clinics and mobile clinics. Clinical Officers run the clinics 80% of the time, but with full time telephone access to a physician. The other 20% of the time, physicians and pediatricians run the

clinics and are able to assess all the difficult cases, make decisions on change of therapy due to treatment failure and offer mentorship.

The entry points into the program is through Voluntary Counseling & Testing (VCT) , Diagnostic Testing and Counseling (DTC), Prevention of Mother To Child Transmission testing (PMTCT) or referral from another health facility. TB prophylaxis is offered to all patients who have no symptoms or history of TB diagnosis and have normal chest radiographs.
Septrin prophylaxis is offered to all patients with CD4 counts less than 200. or TB diagnosis.

ART is initiated in all patients with CD4 counts <200, those with stage 3 or 4 disease regardless of CD4 counts, and all pregnant women with CD4 counts < 350. The first line ARV regimen used is 3TC and d4T or AZT, with NVP or EFV. Second line therapy includes any two Nucleoside reverse transcriptase inhibitors left out in the primary therapy combined with Ritonavir boosted lopinavir (Lp/Rt).

Over 55,000 patients are currently receiving care in AMPATH with 23000 adults being on ARV treatment. An estimated 5.9% of these patients are already on second line having failed the first line. [12]

All laboratory tests are done in the AMPATH reference laboratory with internal and external quality assurance.

In addition to treatment, patients benefit from counseling while nutritional support is given to impoverished patients and their families. They also get farming and micro-enterprise training when deemed necessary.

In the initial phase, some of the patients had to fund their treatment, but the advent of Presidents Emergency Plan for Aids Relief (PEPFAR) and other funds made free treatment possible.

AMPATH data management

All sites complete the same initial and return encounter forms

Initial encounter forms have information on demographic, historical, psychosocial, physical and laboratory data.

Return visit forms have information on intercurrent symptoms, adherence, new diagnosis, laboratory data and drug modifications. Most data is entered into the forms by check boxes to ensure uniformity of information and ease of transfer into the database. These forms are transported to the data centre in AMPATH daily. Any missing data is flagged by a team that cross-checks the forms in the data-room before data entry. Flagged forms are returned to the clinician for correction before entry into database.

The database uses Open Medical Record System (MRS), which is able to hold millions of records. Regular internal audits of database are done and data error has been found to be less than 2%. [41]

6.3 STUDY POPULATION

6.31 Definition of Cases and Controls

Cases were made up of adults in the AMPATH database, found to fulfill the criteria of immunologic treatment failure. Immunologic failure was defined according to the AMPATH protocols, i.e;

1.) Failure of CD4 counts to rise from baseline by 100, or to at least 200 after 6 months of ARV therapy, or

2.) Drop of CD4 counts to pretreatment levels after at least 6 months of good response, or,

3.) A drop of CD4 counts of 25% or more, from the peak count ever achieved .

Controls were drawn from persons in the same database who did not meet the criteria of immunologic treatment failure and showed an increase in CD4 counts of at least 100cells/mm3, or to >200cells/mm3 within first 24 weeks of treatment.

6.32 Inclusion Criteria

1) HIV positive patients aged 18 years and above and initiated on ART in any AMPATH clinic between February 2006 and September 2008.

2) Patients who were ARV naive prior to initiating treatment in AMPATH. (Patients who had used ARVS for PMTCT prior to treatment were considered ARV naive).

6.33 Exclusion Criteria.

Patients with more than 75%of their data missing.

6.4 DATA EXTRACTION

The AMPATH database was reviewed for all patients who were enrolled between February 2006 and September 2008. Those who met the inclusion criteria, and were found to have failed first line therapy were recruited into the study group while those meeting inclusion criteria but without treatment failure were recruited into the control group.

The following information was extracted from the database on both groups of patients:-

1. Age (in years)
2. Sex.
3. Weight (in Kilograms)
4. Marital status.
5. Occupation.
6. Education level.
7. **Year enrolled and duration from enrollment to initiation of therapy.**
8. Clinic site (rural vs urban)
9. Disclosure status at start of therapy.
10. WHO stage at start of therapy.
11. Isoniazid (INH) prophylaxis at start, or prior to start of therapy.
12. History of treatment for TB, before during or after starting therapy.
13. CD4, Haemoglobin, Creatinine (where available)
14. The first line ARV therapy prescribed.
15. Changes of drug prescription due to toxicities.
16. Adherence

DEFINITIONS

Information on adherence was drawn from the adherence assessment recorded at every visit. This assessment consists of one question: "during the last 7 days how many of your antiviral pills did you take?' the available answers are 'none, few, half, most and all'. For this study, adherence was stratified into, perfect adherence (for those with all pills taken all the time) or imperfect adherence (if even one answer is anything other than all).

Disclosure status was defined as disclosed where one had informed another person of his or her HIV status other than the health care giver, or not disclosed where one had not informed anyone else.

Baseline was defined as time of starting anti-retroviral therapy.

6.5. DATA ANALYSIS

All extracted data was analyzed. The data was classified as follows:-

Continuous variables	**Categorical variables**
Age	Gender
Weight	Education level
Duration from enrollment to HAART	Employment status
Duration on 1st line HAART	Marital status
CD4 counts	Disclosure status at start of therapy
Creatinine	INH prophylaxis status
Hemoglobin	1sl line regimen
	Therapy change due to toxicities
	CD4 counts
	Age

The baseline characteristics were compared using student t test for continuous variables , and chi square for categorical variables.

Univariate logistic regression was used to analyze the crude odds ratio (O.R) for different categories of the risk factors. Factors found to be significant at univariate analysis were subjected to multivariate logistic analysis to get the adjusted O.R. All tests were performed at the 0.05 level of significance

7.0 ETHICAL CONSIDERATIONS

The study protocol was presented to the Department of Internal Medicine, University of Nairobi and approved on 26th August 2008. It was then submitted to Kenyatta National Hospital Ethics and research committee, which approved it on 28th October 2008. Moi University Research and Ethics committee also reviewed and approved it. The AMPATH data committee gave a final approval, before the data was finally accessed.

The data used was stored in computerized medical records and all patient identifiers were removed to ensure patient confidentiality.

Results from this study were promptly communicated to the Moi Referral Hospital and AMPATH with recommendations

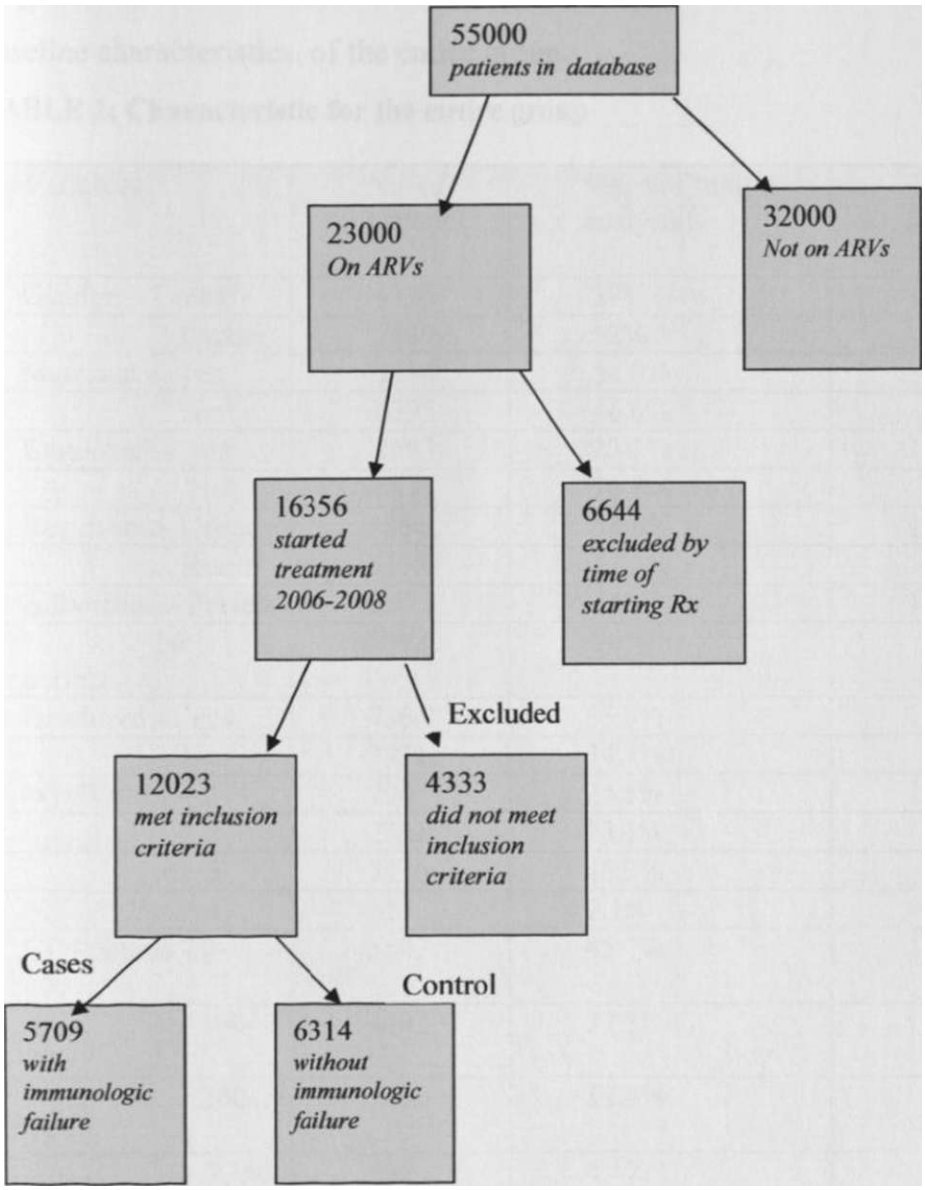
8.0 RESULTS

8.1 RECRUITED SAMPLE

As of December 2008, 55000 patients had been enrolled into the AMPATH clinics. 23000 patients out of these had been started on ARV treatment with 16,356 having been started between February 2006 and September 2008. which was the duration of interest. Those who met the inclusion criteria into our study were 12023, and of these, 5709 had immunologic failure based on at least one out of our three definitions. All the remaining 6314 patients were included into the control arm of the study.

Matching of cases to controls based on time of starting therapy was not done. This was because immunologic failure by our definition turned out to be frequent occurring in about 25% of the treatment cohort. . We established that the mean time of follow up for the two groups was similar at 92 days for cases and 90 days for controls, with median of 88 days for cases and 91 days for controls. It is however appreciated that this similarity cannot be equated to actual matching.

Figure 1: Recruitment flow chart



8.2 CHARACTERISTICS OF INCLUDED PATIENTS.

Sixty two percent of the entire group was female, 76% unemployed. 65% had disclosed their HIV status to someone other than their health care provider and 74% had perfect adherence. In terms of clinical parameters. 53% were in WHO stage 3 & 4, while 73% had CD4 counts below 200. Table 1 summarizes these baseline characteristics, of the entire group.

TABLE 1; Characteristic for the entire group

Variables	No of patients	%age of total analyzed	Total analyzed
Gender:- male	4534	38%	12023
female	7489	62%	
Marriage:- yes	5414	54.0%	11809
No	6395	46.0%	
Employed:- yes	2663	23.2%	11494
No	8831	76.8%	
Residence:- Urban	5865	48.8%	12023
Rural	6158	51.2%	
Adherence:- Perfect	8805	74%	11903
Not perfect	3098	26%	
Disclosed:- Yes	7366	65.3%	11277
No	3911	34.7%	
WHO stage:- 1	2946	24.5%	12018
2	2781	23.1%	
3	5436	45.2%	
4	855	7.1%	
CD4 counts:- 0-100	5503	45.7%	12027
100-200	4492	37.3%	
200-350	1496	12.4%	
>350	532	4.4%	
Treated for TB	2832	42.0%	67344

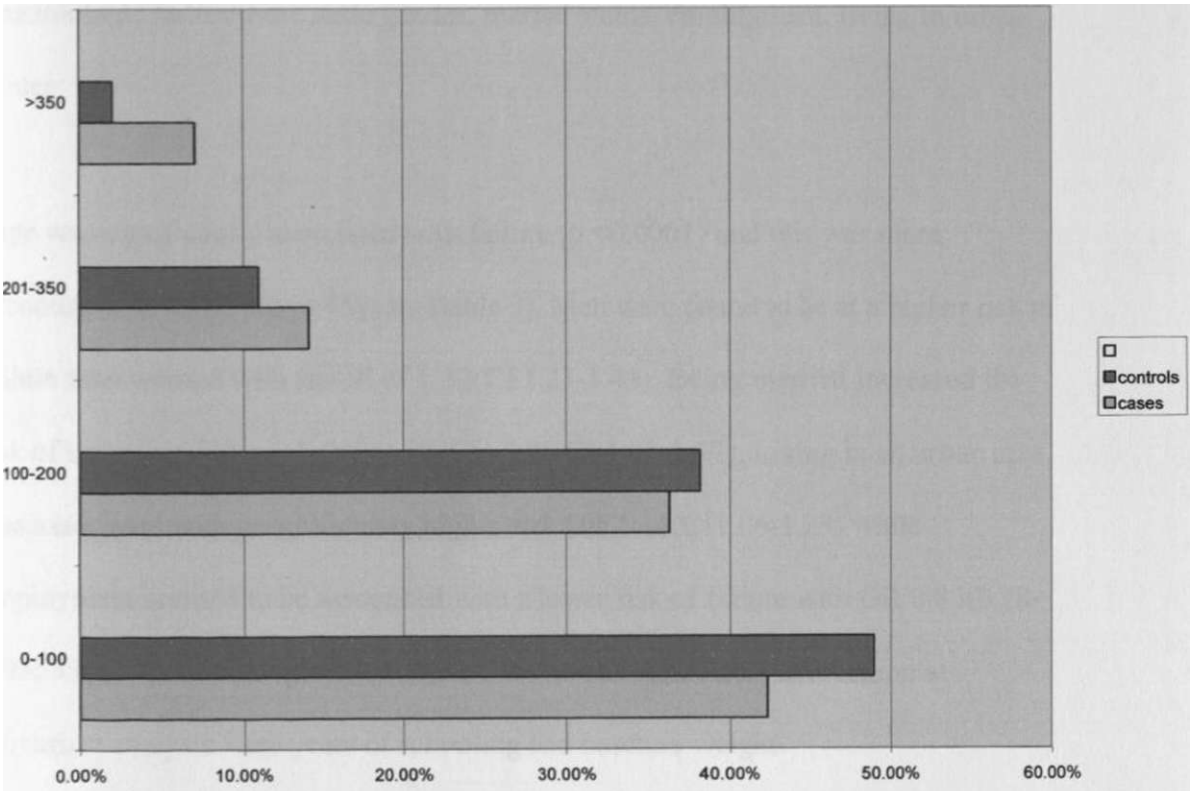
8.3 CHARACTERISTICS OF CASES AND CONTROLS.

At baseline 58.8% of the cases were female, 55% married. 24.7% employed and 53% were residing in urban centers. The cases had a mean age of 39.7 years, mean weight of 56.7 Kg. Perfect adherence was recorded in 72%, and 65% had disclosed their HIV status to someone other than the healthcare provider. Majority of the cases were in WHO stage 3 (44%) and a minority in stage 4. Majority of them had CD4 counts below 200. The mean baseline CD4 count was 149. Amongst the controls, 65.4% were female, 53% married, 21% employed and 50% were residing in urban areas. Their mean age at baseline was 38.6 yrs and mean weight 55Kg. Adherence was perfect in 75 % of them , while 65% had disclosed their HIV status to someone other the health care provider. 49% of these patients were in WHO stage 3, with only 7% being in stage 4. Over 80% of them had CD4 counts less than 200 with only 2% having counts above 350. Their mean baseline CD4 count was 116.
Table 2 and figure 2 summarize these findings.

Table 2: Characteristics of cases and controls

Variable	Cases	Controls
Age (mean)	39.7yrs	38.6yrs
Gender: Female	3358 (58.8%)	4131 (65.4%)
Male	2351 (41.2%)	2183 (34.6%)
Marriage yes	3089 (55.2%)	3306 (53.2%)
No	2506 (44.8%)	2908 (46.8%)
Employed: Yes	1342 (24.7%)	1321 (21.8%)
No	4098 (75.3%)	4733 (78.2%)
Residence: Urban	3024 (53%)	3134 (49.6%)
Rural	2685 (47%)	3180 (50.4%)
Adherence: Perfect	4086 (72.8%)	4719 (75%)
Not perfect	1527 (27.2%)	1571 (25%)
Disclosed : Yes	3499 (65.6%)	3867 (65.1%)
No	1837 (34.4%)	2074 (34.9%)
Treated for TB	1325 (41.3%)	1507 (42.8%)
WHO stage: 1	1439 (25.3%)	1252 (19.9%)
2	1207 (21.2%)	1423 (22.6%)
3	2550 (44.8%)	3113 (49.5%)
4	494 (8.7%)	505 (8%)
CD4 counts at start of therapy: 0-100	2416 (42.3%)	3087 (48.9%)
100-200	2078 (36.4%)	2414 (38.2%)
200-350	809 (14.2%)	687 (10.9%)
>350	406 (7.1%)	126 (2%)
1st Line regimen : Effavirenz	1707 (24%)	1408 (26%)
Nevirapine	5417(76)	3989 (74%)

Figure 2; Baseline CD4 counts.



8.4 SOCIO-DEMOGRAPHIC FACTORS AND FAILURE

At univariate analysis, socio-demographic factors found to be associated with immunologic failure were male gender, marital status, employment, living in urban center

Age was significantly associated with failure ($p < 0.0001$) and this was more pronounced in those above 45years (table 3). Men were found to be at a higher risk of failure than women with an OR of 1.32(CI 1.23-1.43). Being married increased the risk of treatment failure slightly with OR 1.08(CI 1.01-1.17). Living in an urban area was associated with a significantly higher risk OR 1.14(CI1.06-1.23) while employment seemed to be associated with a lower risk of failure with OR 0.85(0.78-0.93). Other socio demographic factors that showed significant association at univariate analysis were years of schooling and baseline weight.

Table 3 summarizes these associations.

Table 3: Association of socio-demographic factors with failure.

Variable	*Level*	*Cases n(%)*	*Controls n(%)*	*OR[95% CI]*	*pvalue*
Gender	female	3358(58.8)	4131(65.4)		
	male	2351(41.2)	2183(34.6)	1.32(1.23-1.43]	<.0001
Married	no	2506(44.8)	2908(46.8)		
	yes	3089(55.2)	3306(53.2)	1.08(1.01,1.17]	0.0288
Employed	No	4098(75.3)	4733(78.2)		
	yes	1342(24.7)	1321(21.8)	0.85(0.78,0.93]	0.0003
Urban-residence	no	2685(47.0)	3180(50.4)		
	yes	3024(53.0)	3134(49.6)	1.14(1.06,1.23]	0.0003
Age	15-29	608(11.1)	822(13.6)		<0001
	30-45	3461(63.2)	3798(62.9)		
	45+	1411(25.7)	1417(23.5)		
	Mean (yrs)	39.7	38.6		<0.0001
Weight	Mean (kg)	56.7	55.0		<0.0001
Years of schooling	Mean(yrs)	8.7	8.5		0.0068

8.5 ASSOCIATION OF THERAPEUTIC FACTORS WITH FAILURE

Perfect adherence reduced the risk of failure with an OR 0.89[CI 0.82-0.97]. Use of Efavirenz based first line regimen was associated with a significantly lower risk with an OR of 0.89[CI 0.80-0.94]. Time from enrollment to start of therapy, disclosure status and experience of toxicity requiring change of therapy did not show any significant association with immunologic failure. Having received TB prophylaxis showed a trend towards protection from immunologic failure.

Table 4: **Therapeutic factors and failure**

Variables	Levels	Cases (%)	Controls (%)	OR (95% CI)	P value
ARV adherence perfect	no	1527(27.2)	1571(25.0)		
	yes	4086(72.8)	4719(75.0)	0.89(0.82,0.97]	0.00057
Time from enrolment to start of Rx	Mean (days)	90.5	94.8		0.1557
TB Prophylaxis	no	90(44 1)	66(36.7)		
	yes	114(55.9)	114(63.3)	0.73(0.49,1.11]	0.1379
HIV Status Disclosed	no	1837(34.4)	2074(34.9)		
	yes	3499(65.6	3867(65.1)	0.98(0.91,1.06]	0.5902
Treated for TB	no	1887(58.7)	2015(57.2)		
	yes	1325(41.3)	1507(42.8)	0.94(0.85-1.03)	0.2020
Toxicity experienced	no	5325(93.3)	5906(93.5)	1.04(0.90,1.21]	0.5595
	yes	384(6.7)	408(6.5)		
1ai Line Regimen	EFV	1707 (24)	1408 (74)	0.89(0.80,0.94)	0.0064
	NVP	5417(76)	3989 (26)		

Association of clinical factors with failure.

At baseline, patients who went on to develop immunologic failure had higher mean CD4 counts than controls. This was statistically significant with a p value <0.0001. The controls however attained a significantly higher maximum CD4 counts than the cases.

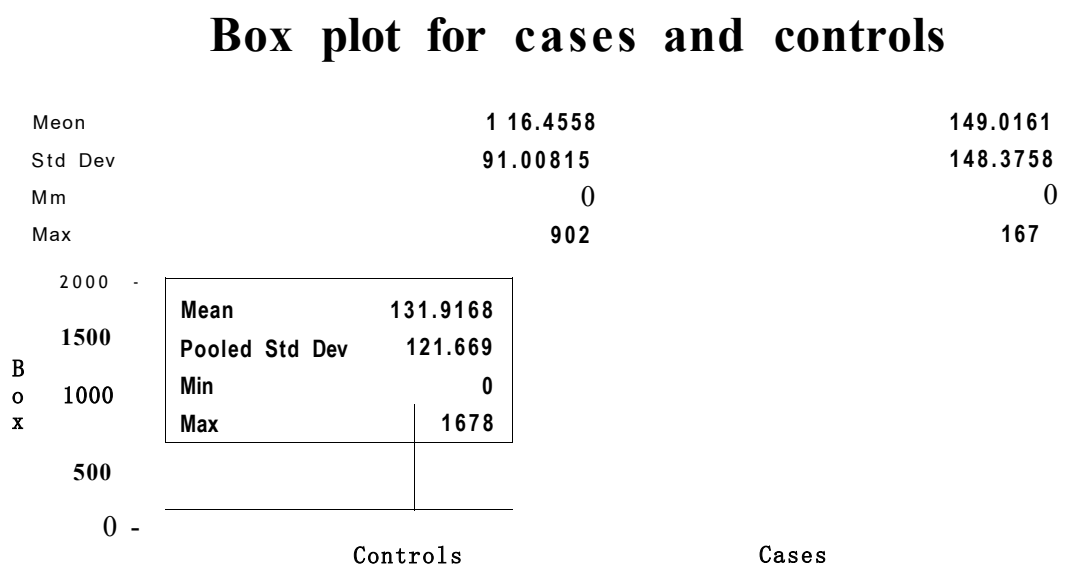
There was also a significant association of baseline or first ever recorded WHO stage with treatment failure.

Table 5: Clinical factors and immunologic failure

Variable	category	Cases	Controls	P value
Baseline or first recorded WHO stage.	1	1439(25.3)	1251(19.9)	<0001
	2	1207(21.2)	1423(22.6)	
	3	2550(44.8)	3113(49.5)	
	4	494(8.7)	505(8.0)	
Baseline cd4 category	0-100	2416(42.3)	3087(48.9)	<.0001
	101-200	2078(36.4)	2414(38.2)	
	201-350	809(14.2)	687(10.9)	
	350+	406(7.1)	126(2.0)	
CD4 Maximum category	0-100	754(13.2)	0(0.0)	<0001
	101-200	1862(32.6)	800(12.7)	
	201-350	1848(32.4)	2528(40.0)	
	350+	1245(21.8)	2986(47.3)	

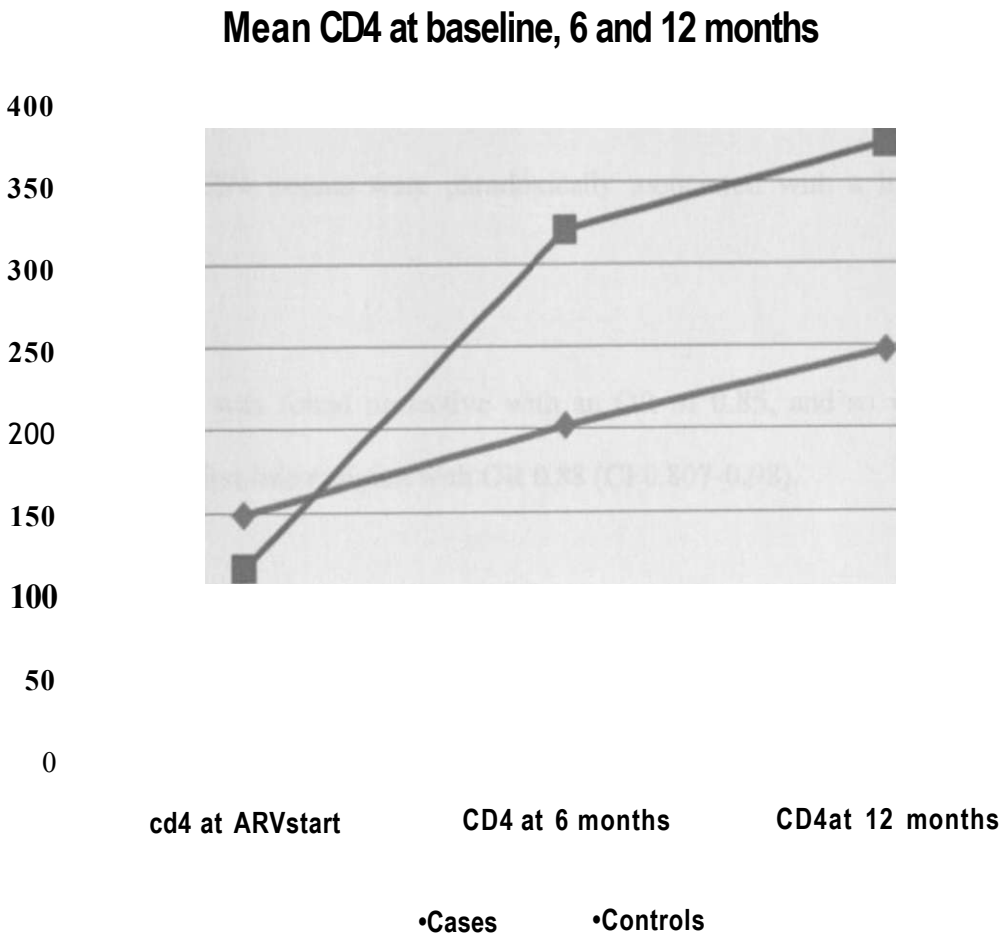
Of note, is the fact that there was a much higher variability of CD4 counts at baseline in the cases than the controls with counts ranging from 0 to 1678 compared to 0 to 902 in the controls. This is demonstrated in figure 3 below.

Figure 3: Baseline CD4 counts



In both cases and controls, mean CD4 counts increased over time . However, the increase in the controls was very rapid in the first 6 months compared to that seen in the cases. Thereafter, the rate of increase in both groups seemed to be equal.

Figure 4 summarizes the changes in CD4 counts over time in cases and controls.



8.6 ASSOCIATIONS ON MULTIVARIATE ANALYSIS

At multivariate analysis factors that were found to be independently associated with immunologic failure, were, male gender with an O.R 1.28(95%C.I 1.18-1.385), age at start of ARVs OR 1.01 (95%CI 1.008-1.017) and urban residence. When age was analyzed as a categorical variable, the age group above 45 years was found to be most significantly associated with increased risk in comparison to those 18years to 29years.

Higher baseline CD4 counts were paradoxically associated with a higher risk of failure.

Perfect adherence was found protective with an OR of 0.85, and so was being on Effavirenz based first line regimen with OR 0.88 (CI 0.807-0.98).

Table 6: Associations at multivariate analysis with age as continuous variable.

Variable	*Level*	*OR[95% CI]*	*p-value*
male	female	1.28 [1.18-1.39]	<0001
Married	no	1.03 [0.948- 1.122]	0.4671
Employed		0.97 [0.878- 1.068]	0.5216
Urban residence		1.10 [1.020-1.185]	0.0136
WHO stage	1	1.14 [0.965- 1.336]	0.1269
	2	0.95 [0.811-1.119]	0.5561
	3	0.94 [0.805-1.087]	0 3846
Baseline CD4	0-100	3.7 [3.02-4.67]]	<0001
	101-200	3.4 [2.78-4.33]]	<0001
	201-350	2.56 [2.06-3.22]]	<0001
ARV adherence perfect		0.85 [0.777-0.921]	0.0001
Age at start of ARVs		1.01 [1.007- 1.015]	<0001
Weight at start of ARV		1.01 [1.005 - 1.012]	<0001
; 1" line ARV - EFV		0.88[0.807-0.981]	<0.018

Table 7: Associations on multivariate analysis with age categorized

Variable	*Level*	OR/95% *CI]*	*p-value*
male	female	1.298(1.20-1.41]	<.0001
Urban residence		1.09 [1.009-1.175]	0.0277
WHO stage	1	1.15(0.977-1.359]	0.0919
	2	0.97 [0.823 -1.140]	0.7007
	3	0.95 [0.815-1.105]	0.4998
Baseline CD4(>350)	0-100	3.846(3.076-4.807]	<.0001
	101-200	3.571 [2.816-4.405]	<.0001
	201-350	2.564 [2.04-3.298]]	<.0001
ARV perfect adherence		0.84 [0.775-0.921]	0.0001
Age group (>45yrs)	15-29	1.28 [1.17-1.46]	0.0003
	30-45	1.04(0.96-1.14]	0.3525
Weight at start of ARV		1.01 [1.004-1.012]	<.0001
First-line regimen	effavirenz	0.89 [0.807 - 0.981]	0.0189

Table 8: Sub-group Analysis excluding cases diagnosed by failure of CD4 counts to rise by 100 at 6 months of treatment.

Variable	*Level*	*OR[95% CI]*	*p-value*
male	female	1.098 [1.01 -1.204]	0.0483
Married	no	0.94 [0.858-1.022]	0.1404
Employed		1.09 [0.979-1.206]	0.1190
Urban resident		1.408[1.298-1.534]	<.0001
Age group (>45)	18-29	1.265 [1.103-1.461]	0.0009
	30-45	1.298 [1.144-1.466]	<.0001
ARV perfect adherence		0.80 [0.73-0.89]	<.0001
Baseline CD4	0-100	2.70(2.218-3.294]	<.0001
	101-200	1.46 [1.279-1.668]	<.0001
	201-350	1.11 [1.014 -1.220]	0.0240

This sub-group analysis was done in cases who had dropped their CD4 counts either by 25% from peak or to pretreatment levels.

In this subgroup, male gender, urban residence, age above 45years and high baseline CD4 counts were still significant factors associated with immunologic treatment failure.

9.0 DISCUSSION

9.1 INTRODUCTION.

The AMPATH cohort , is the largest treatment cohort of HIV patients in the country with both rural and urban centers. It therefore does give a good representation of HIV treatment issues in the country. This secondary data analysis of 12023 patients was used to describe some factors that are related to immunologic failure in this cohort.

Majority of the patients included in this analysis were female , unemployed and young with a mean age of 39yrs. This is in keeping with most studies that have been done in this set up [5,6]. Over 80% of them started antiretroviral therapy with advanced disease with CD4 counts below 200. This can be explained by the fact that CD4 counts of 200 have been the cut off for starting treatment in both the national and AMPATH guidelines. Of note is the lack of correlation between CD4 counts and WHO clinical stage with 82% of the patients having counts below 200 compared to only 52% in WHO stage 3 and 4. This implies that in settings where antiretroviral treatment is initiated purely based on WHO stage, many patients who are classified as stage 1 or 2 are actually unnecessarily delayed from starting therapy.

9.2 SOCIO-DEMOGRAPHIC FACTORS AND TREATMENT FAILURE

This study documented an independent association of gender with treatment failure, with males being at higher risk than females. The association was independent of age. adherence and baseline CD4 counts. This is in keeping with an earlier local study done by Wools Kaloustin et al that showed a slower CD4

response, earlier tendency to failure and a higher mortality and loss to follow up in males as compared to females [5]. Rajasekaran et al in a similar study in India , also documented an association of male gender with failure, with a hazards ratio of 3.5 (95%CI 1.6-3.4). In his study however he also noted that the men were older which may have compounded the risk [37]. An analysis looking at the relationship of gender and treatment failure in the Eurosida cohort did not find any significant association of the two. This study however was different from ours in that the females were a minority, and they used virologic parameters to define their endpoints [28]. It is possible therefore that the apparent increased risk of failure in men is only in terms of immunologic failure for unclear reasons. This nevertheless does suggest poorer treatment outcomes for men and hence a need for closer monitoring.

Older age was significantly associated with immunologic failure at univariate analysis. This association was maintained at multivariate analysis but only for the age-group 15-29 years in comparison to >45years with an OR of 0.78(CI 0.684-0.895). Analysis for differences in age with regards to gender or baseline clinical status was not done and therefore it is difficult to explain this association fully. Other investigators that have looked at age and treatment failure have found conflicting results. Michelaud et al found significantly slower rise in CD4 counts with every 5 yr increase in age. He also showed an overall poorer CD4 recovery in patients aged over 45years [29]. Kamya et al in Uganda did not find any significant association of age with treatment failure. His study however was looking at virologic failure [35]. It is possible that this apparent association of age with immunologic failure may be a result of an interplay between the physiological decline in immunity with age, increased susceptibility to infections and increased rate of co-morbidities. The latter is supported by work done by G Orlando et al. which demonstrated a higher rate of co-morbidities in patients above 50years [30].

The risk of immunologic failure was increased in patients from urban areas. This association was stronger at univariate than multivariate analysis, but still statistically significant. Rajasekaran et al in India documented a similar finding [37], The reasons for this association are still unclear though high risk behaviour in urbanites may be one of them.

Although employment and marital status were associated with immunologic failure at univariate analysis, this association was lost on multivariate analysis and was probably due to their effects on adherence.

9.3 CLINICAL FACTORS AND IMMUNOLOGIC FAILURE

Baseline WHO stage was only associated with immunologic failure on univariate analysis. Monforte et al had documented a higher risk of treatment failure in patients starting therapy with higher WHO stage, while Kamya et al had found no association [32, 35].

It is likely that the effect of baseline WHO stage on treatment outcome is through its effect on adherence and hence the lack of significance when this is controlled for.

Patients who started treatment with higher CD4 counts were found to be at higher risk of treatment failure. All previous studies that looked at the association of baseline CD4 counts with treatment failure either showed a reduction in risk in those who started with higher CD4 counts or no association [8,41,42,46,]. This study's finding cannot be explained by adherence since it was seen even at

multivariate analysis. It is therefore likely to be a spurious finding caused by a selection bias.

It was suspected that the cause of the bias was the inclusion of patients who failed to increase their baseline CD4 counts by 100 in the first 6 months, as cases. This is because those starting therapy with very high counts may not increase their counts at the same rate as those starting with lower CD4 counts and therefore likely to introduce a misclassification bias. To confirm this, a sub analysis that excluded this group of patients was done as reported in table 8. This subgroup analysis of 3998 still found higher baseline CD4 counts significantly associated with increased risk of immunologic failure. The definition of immunologic failure was therefore not the source of bias.

Patients starting therapy with higher CD4 counts have been shown to have a survival advantage over those who start therapy with lower counts. On the other hand, the likelihood of treatment failure increases as the duration on therapy progresses. This is a major source of selection bias that could only be prevented by matching to time on therapy. Unfortunately, this was not done in this study because the prevalence of immunologic failure as per the definitions used was much higher than expected at >25%. The conclusion that high baseline CD4 counts are associated with higher rates of immunologic failure can therefore not be made from this study.

9.4 THERAPEUTIC FACTORS AND IMMUNOLOGIC FAILURE.

The independent association of adherence with immunologic failure was evident. Though the level of adherence recorded was high, it is important to note that this was self reported adherence and may not be accurate. It is however unlikely that more patients were more inaccurate in one group than the

other and these results are therefore reliable. Kamya et al in Uganda did not establish any association of adherence with virologic failure. His study though had much fewer patients and they had almost a 100% adherence [35].

Use of Efavirenz based regimen was associated with a significantly lower risk of immunologic treatment failure than Nevirapine based regimens in this study. This is supported by a study done in Uganda by Kamya et al that showed similar results [35]. However, a study done in India showed a higher risk of failure in patients on Efavirenz than on Nevirapine [37]. The role of differences in pharmacogenomics as have been described previously in relation to Effavirenz may explain these findings [26].

TB prophylaxis with Isoniazid did not show a statistically significant association with immunologic failure. It however did show a tendency towards reduced risk and may probably have been significant had the missing data been less. The association may be because many of the patients that are put on Isoniazid prophylaxis are healthy and start using it earlier than antiretroviral treatment, hence have time to perfect their adherence.

9.5 CO-MORBIDITIES AND IMMUNOLOGIC FAILURE

Neither TB, nor hematological factors were found to be significantly associated with failure. Data on hematological factors was however available in only 1% of the analyzed group and was therefore unreliable.

Rajasekaran et al had shown a 3 times higher risk of failure in patients previously treated for TB [37]. The fact that in this analysis only 50% of the patients had data on Tb treatment could have masked any association that may have existed.

9.6 STUDY LIMITATIONS

1. Being a secondary data analysis, not all the data was available and hence analysis for variables such as hematological factors was not feasible. It was also not possible to establish the average time to failure for the same reasons.
2. The definition of immunologic failure as it stands currently is limiting as it is unable to pick failure before 6 months of treatment.
3. Lack of viral loads makes it difficult to generalize these results to those with virologic failure.
4. Antiretroviral drug sensitivity testing was not done for any of these patients and hence the role of drug resistance is not addressed by this study.

10.0 CONCLUSION

This study established that, in this Western Kenya treatment cohort of HIV patients, poor adherence, male gender, advancing age, and urban residence were risk factors for immunologic treatment failure. It also does raise the possibility of differences in efficacy of Nevirapine versus Effavirenz based regimen in our set up.

11.0 RECOMMENDATIONS

Perfect adherence should be emphasized in all patients on HIV treatment.

Male patients, urbanites and those above 45 years old should be monitored more closely for treatment failure.

An analysis is done exploring the reasons for the increased risk of treatment failure in males urbanites and older patients.

A randomized controlled trial addressing the efficacy of Nevirapine versus effavirenz based ARV regimens in our populations should be done.

Laboratory data entry into the AMPATH database should be improved.

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