TREATMENT OUTCOMES OF SECOND LINE ANTIRETROVIRAL THERAPY

IN MBAGATHI DISTRICT HOSPITAL

COMPREHENSIVE CARE CLINIC

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Declaration

I declare that this dissertation is my original work and has not been presented for the award of a degree at any other university

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DEDICATION

Dedicated to almighty God for making the whole project a success. My wife Jane Murugi and my daughters Abigael Ndanu and Angel Wambui for their constant support towards the realization of this dream. To my parents, Kiio Musyoki and Pauline Muwe.

ACKNOWLEDGEMENT

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ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
AIDS	Acquired Immunodeficiency Syndrome
ABC	Abacavir
ARVs	Antiretrovirals
ART	Antiretroviral Therapy
AZT	Zidovudine
CD4	Cluster of Differentiation Type 4
CHW	Community Health Worker
d4T	Stavudine
ddI	Didanosine
DRV	Darunavir
EFV	Efavirenz
FDC	Fixed Dose Combination
HIV	Human Immunodeficiency Virus
IRIS	Immune Reconstitution Inflammatory Syndrome
KDHS	Kenya Demographic Health Survey
LFU	Lost to Follow Up
LPV/r	Lopinavir/ritonavir
MDH-CCC	Mbagathi District Hospital, Compressive Care Clinic
MTRH	Moi Teaching and Referral Hospital
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitors

NRTI	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
OIs	Opportunistic Infections
PI	Protease Inhibitor
PMTCT	Prevention of Mother to Child Transmision
TB	Tuberculosis
TDF	Tenofovir
TWG	Technical Working Group
UNAIDS	United Nations, Acquired Immunodeficiency Syndrome
WHO	World Health Organization

ABSTRACT

Background

Human Immunodeficiency Virus (HIV) is one of the leading causes of morbidity and mortality in sub-Saharan Africa. In Kenya, an estimated 1.5 million people are living with HIV. Antiretroviral Therapy (ART) has been in use in public health facilities since 2003[1]. ART scale up has significantly reduced morbidity and mortality. As at December 2012, there were 606,793 patients on ART in 1405 sites country wide. It is estimated that 3.2% of these are on second line ART corresponding to a total of 19,417[2]. As more patients are put on ART, the number requiring second line therapy has continued to increase. The aim of this study was to determine treatment outcomes of patients on second line ART at Mbagathi District Hospital, Compressive Care Clinic (MDH-CCC)

Objectives

The primary objectives of this study were: to determine the clinical, immunologic and virologic outcomes of patients on second line ART and to determine their adherence using pharmacy refill records. A subset of the population was used to determine retention in care after switch to second line ART.

Methodology

This was a retrospective observational cohort study. Patients who had been switched to second line ART between January 2005 and March 2012 were studied to determine clinical, immunologic and virologic outcomes; and to determine levels of adherence. A subset of this population who had been switched to second line ART between January 2008 and March 2012 were studied to determine retention in care.

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Results

We found 93% of patients had successful clinical treatment outcomes while those with successful immunologic outcomes were 90%. We found 87% of patients had adequate viral suppression. The proportion of patients with satisfactory adherence was 98%. Out of the patients with virologic failure, only 4 (11.8%) had both virologic and immunologic failure. Another 4 (11.8%) had both clinical and virologic failure while only 1 had clinical, immunologic and virologic failure. Unsatisfactory adherence (<95%) was noted in 2 patients (5.9%) with virologic failure. We found that immunologic criteria would fail to identify 88% of patients with virologic failure. There were 161 (82%) patients retained in care after a mean duration of follow up of 35 months.

Conclusion

We showed that second line ART is associated with good clinical, immunologic and virologic outcomes in MDH-CCC as expected. We found that most patients had satisfactory adherence to their therapies. Retention in care after switch to second line ART was high.

CHAPTER 1: INTRODUCTION

1.1 Background

Human Immunodeficiency Virus (HIV) is one of the leading causes of morbidity and mortality in sub-Saharan Africa. According to the UNAIDS/WHO report on the Global AIDS pandemic, 2011 HIV has spread to every country in the world. By December 2010, 34 million people were estimated to be infected with HIV[3]. In Kenya, HIV/AIDS was declared a national disaster in 1998. Since then, resources have been mobilized to contain the pandemic. ART has been in use in public health facilities since 2003[1]. As at December 2012, there were 606,793 patients on ART in 1405 sites country wide. It is estimated that 3.2% of these are on second line ART corresponding to a total of 19,417[2]. With ART scale-up, there is increase in the number of patients requiring second line ART. This has been shown to be due to treatment failure to first line regimen or development of toxicities or co-morbidities[4]. There are many mothers who are exposed to nevirapine through PMTCT and when they require ART, they cannot be treated with first line regimen due to the previous exposure. There was no documentation of the treatment outcomes of patients on second line antiretroviral therapy in Kenya prior to this study. The findings of this study gave important information for planning and budgeting for care and treatment services for these patients.

CHAPTER 2: LITERATURE REVIEW

Following HIV seroconversion, there is marked variability in disease progression, in the absence of ART. Antiretrovirals (ARVs) have been developed to slow down the disease progression[5]. Effective ART involves combination of three or more different ARVs, which significantly slows disease progression and delays the onset of AIDS in HIV-positive people.

2.1 HIV in Kenya

The first HIV case in Kenya was diagnosed in 1984. The number of people living with HIV has continued to increase. Approximately 1.5 million people have died from this disease in the country. According to the Kenya Demographic and Health Survey (KDHS) of 2008, the HIV prevalence was 6.3% among Kenyans aged 15 – 49 years compared to 6.7% in 2003[6]. The national prevalence is 6%[3] and the number people living with HIV as at December 2012 was estimated at 1.5 million. It is estimated that 1.2 million children have been orphaned by AIDS; and in 2010 approximately 85,000 people died from AIDS-related illnesses[3].

2.2 First line regimens

WHO revised its recommendations of ART management in adults and adolescents in 2009[7]. The Kenya National ART Guidelines were revised in November 2011 and these recommendations were considered. The choice of preferred regimens is based on efficacy, durability, tolerability (potential toxicities), ease of use (availability of fixed dose combination - FDC), cost of drugs and laboratory monitoring requirements, availability of regimen and continuity of supply to meet demand; and potential for maintenance of future treatment options[7].

A combination of tenovofir (TDF) + lamivudine (3TC) is the preferred Nucleoside Reverse Transcriptase Inhibitor (NRTI) backbone. Zidovudine (AZT) is recommended as part of the first line regimen in pregnant women because of the long term experience with it in this situation. Due to cost, abacavir (ABC) use in adult patients in Kenya should be limited to those with

moderate to severe renal impairment where it is preferred above the other NRTIs. Stavudine (d4T) use is no longer recommended as an option in patients starting first line ART. However, d4T continues to be used by a large proportion of patients already on ART. These patients should be monitored for toxicity and treatment reviewed if present. d4T continues to have a role as part of second-line therapy where AZT is not tolerated. With regard to the Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) choice, efavirenz (EFV) is preferred in TB/HIV co-infection. Nevirapine (NVP) is preferred in women who wish to conceive or are at risk of pregnancy and are not on effective contraception[8].

2.3 Second line regimens

Second line regimens are developed mainly for patients failing first line regimen. Few patients may be put on second line therapy if they develop toxicities or co-morbid conditions and lack options for modification among the first line regimens. Second line regimens are dependent on the regimen used as first line. Initial second line regimens involved changing all the three drugs. When d4T was a main drug in first line regimen combined with 3TC for the NRTI backbone, the recommended second line regimens included AZT, didanosine (ddI) and a protease inhibitor (PI) to replace the NNRTI.

According to the current National ART Guidelines, patients who are on AZT or d4T are changed to TDF. Patients on TDF for first line are changed to AZT. This is guided by the fact that when on TDF, the viral mutation K65R increases the viral susceptibility to AZT[9]. TDF does not accumulate Thymidine Analogue mutations (TAMs) which render other thyminide analogues ineffective. Use of d4T is not recommended due to toxicities especially the associated neuropathy, lactic acidosis and lipodystropy. However, it may be used in patients unable to tolerate AZT eg due to severe anaemia[8].

When wild type virus is exposed to 3TC in first line regimen, the common mutation that occurs is M184V. This occurs early but also renders the mutant virus hypersusceptible to AZT. 3TC

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associated resistant viruses have poor replication capacity compared to wild type virus[10]. In resource-limited settings, WHO recommends 3TC to be included in both first and second line regimen and this has been adopted in the Kenya National ART Guidelines.

NNRTIs have a low genetic barrier to resistance. A single mutation in this class eg K103N occurring in a patient on NVP will confer resistance to EFV[11]. The National Guidelines recommend the NNRTI in first line regimen to be changed to a PI. Lopinavir/ritonavir (LPV/r) combination is the preferred PI. If the patient is intolerant to LPV/r, boosted atazanavir (atazanavir/ritonavir – ATV/r) can be used instead[8].

Patients who may not be able to tolerate the above standard second line regime may be put on a non-standard second line regimen. The National Guidelines recommend choice of antiretroviral therapy from ddI, d4T, ABC and ATV. Some patients may require a PI based regimen as their first line regimen (e.g. after severe rash with the NNRTI class). If these patients fail treatment, national therapeutic committee has been consulted by NASCOP for salvage therapy[8].

2.4 Salvage/Third line Regimen

To avoid the need for post second-line (salvage) ART, health care workers should work together with patients to ensure maximum durability of the first line and where this fails the second line regimens. In resource-limited settings, patients requiring salvage regimen are challenging because individualized approach to treatment is required. The regimens are costly and are unlikely to be widely available. There is demand for increased adherence and the monitoring tools are costly and less readily available (viral load and resistance testing). The care for these patients requires specialized healthcare worker expertise and they have a greater likelihood of drug interactions. For these reasons, the National Guidelines recommend clinicians and their patients to aim at the maximum benefit out of early treatment.

A technical working group (TWG) to provide guidance on the management of complex patients including patients failing second-line ART has been set up by NASCOP. General principles for

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the management of patients failing second line ART are that patients continue on the failing regimen until a full third line regimen is available as recommended by the national TWG. Third line regimens should contain at least two fully active drugs for durable, potent virologic suppression. Third-line regimen choice must be guided by resistance testing[8]..

3TC associated resistant viruses have poor replication capacity compared to wild type virus. 3TC should be maintained in patients requiring third-line regimens[10]. Patients failing TDF may still benefit from continuation of TDF despite the presence of the characteristic mutation, K65R. Due to the limitation of resources, the National Guidelines adopt a public health approach. Resistance testing may not be available to most patients and salvage regimen is worked out from known resistance patterns Based on current standardized treatment regimens, majority of patients are likely to achieve full virologic suppression with a regimen of DRV/r plus RAL plus 3TC +/- TDF[8].

Currently, patients have to pay for third line regimen hence this would be inaccessible to the majority of patients. In Kenya, there are no treatment options beyond the drugs recommended for third-line treatment. The Treatment Guidelines recommend patients be made aware that this really is the last opportunity for an effective regimen. Adherence to this treatment must be supported to the largest extent possible, both at facility and community levels. Patients should not start third line drugs unless fully prepared and are ready for the treatment. Monitoring requirements are the same as for other patients. Directly observed therapy should be instituted for the first 3 months of treatment. This should involve engaging a family member or a community health worker (CHW) to provide support. Adherence must be reviewed at each visit, both with the CHW/family member and with the patient.

2.5 Treatment Failure

The goals of ART include maximal and durable suppression of viral replication to prevent development of HIV drug resistance and treatment failure, restoration and/or preservation of

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immunologic function, reduction of HIV-related morbidity and mortality, improvement of the patient's quality of life including prevention of unpleasant adverse drug effects of ARVs and prevention of onward transmission of HIV infection[8]. Treatment failure is inability to achieve the goals of therapy with ART.

Treatment failure is the main reason that leads to switch to a second line regimen. Other reasons include toxicity and co-morbidities eg TB and pregnancy. In his Masters in Medicine Thesis, Owour A O studied reasons for treatment modification at KNH-CCC. He found that 12.9% had been switched to second line regimen and all were due to treatment failure[4].

2.5.1 Determination of treatment failure

ART failure is determined by use of clinical, immunological and virologic parameters.

a) Clinical Failure

Soon after initiation of ART, there may be appearance of new clinical signs and symptoms due to drug side effects or immune reconstitution inflammatory syndrome (IRIS). Later, signs and symptoms may be due to new opportunistic infections or the common infections. There is a significant decrease in morbidity and mortality as patients continue ART[12].

Clinically, treatment failure occurs if there are new-onset opportunistic infections (OIs) or malignancies. It also occurs if there is recurrence of previously treated OIs after at least six months of ART or downgrading of WHO classification in the course of follow up. Unintentional weight loss in a patient who was doing well on ARVs without any overt signs and/or symptoms should trigger suspicion of regimen failure[8].

b) Immunologic failure

Management with ART is usually accompanied by an increase in CD4 count of ≥50 cells/microL at four to eight weeks. This is followed by slower incremental increases of 50 to 100

cells/microL in first year[13]. There after an increase of 20 to 50 cells/microL per year for the next 3-5 years is expected[14].

CD4 cell counts may increase even in patients who do not attain viral suppression. Various hypotheses for this observed immunologic benefit in the face of ongoing viremia have been proposed. These include enhanced HIV-directed immune responses, diminished cellular activation, decreased viral replication capacity, and preservation of non-syncytium-inducing virus strains[15]. However, this immunologic benefit is usually lost after approximately three years of continuous viremia[16].

Immunologic failure is defined as a persistent decline in CD4 count after a period of immune reconstitution. Immunologic failure is present if the CD4 count falls to or below pre-ART level or falls by 30% or more from treatment peak value or remains persistently below 100 cell/mm3 after at least 12 months of effective ART[8].

c) Virologic Failure

Viral load reduction may be more rapid in patients with higher CD4 cell counts, in those with lower levels of baseline viremia and in those who are treatment-naive. Effective therapy should result in at least a 10-fold (1.0 log10) decrease in HIV-1 RNA copies/mL in the first month. This is followed by suppression to less than 50 copies/mL by 24 weeks[17]. Acute illness and vaccinations can cause a transient increase in the viral load. Viral suppression is essential in lowering the chronic inflammatory state and decreasing rate of transmission. Effective antiretroviral therapy reduces the sexual transmission of HIV in HIV-serodiscordant couples by more than 96%.[18].

Virologic failure is defined either as primary failure to achieve a viral load <50 copies/mL or any sustained recurrence of viremia to >50 copies/mL after initial viral suppression. Isolated episodes of low-level viremia ("blips") of between 50 and 500 copies/mL are not predictive of subsequent

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virologic failure. Consistent elevations to more than 50 copies/mL meet a strict definition of virologic failure[17]. Guidelines for Antiretroviral Therapy in Kenya give cut off viral load levels of 1000 copies/mL for treatment failure.[8] Treatment failure occurs following development of resistance to antiretrovirals (ARVs)

2.5.2. Factors Contributing to ART Resistance and Treatment failure

The following factors are associated with ART resistance leading to treatment failure.

a) Adherence

Non-adherence is a leading cause of ART treatment failure[8]. Patients need to take a minimum of 95% of prescribed antiretroviral doses in order to avoid resistance development. Paterson DL et al did a study on a study on adherence to protease inhibitor therapy and outcomes in patients with HIV infection. He found that patients taking 95% or more of their doses only had a documented virologic failure in 22% of the cases compared to 80% of the patients taking less than 80% of their doses[19]. In her Masters of Medicine thesis, Kamano J H studied all previously, treatment naïve patients started on ART and subsequently diagnosed to have treatment failure from AMPATH medical database. Poor adherence was found to be a risk factor for immunologic treatment failure.

b) HIV biology

HIV has high rates of replication, with more than 1×10^9 virions produced daily. The Reverse transcriptase genome is error-prone. The high rates of replication combined with frequent introduction of mutations during each round of replication leads to the frequent occurrence of randomly generated mutations, some of which confer drug resistance. The resulting population of genetically related, but distinct, HIV variants in a patient is referred to as a "quasispecies".

c) Genetic barriers to resistance

HIV can develop high-level resistance to some drugs with only a single mutation, while other drugs require multiple mutations. With a single mutation, drugs with low genetic barrier to resistance lead to high levels resistance. A single mutation eg K103N occurring in a patient on nevirapine will confer resistance to efavirenz[11]. High genetic barrier to resistance among protease inhibitors requires accumulation of multiple mutations to render the drugs ineffective.

d) Regimen potency

The potency of an individual drug or a combination of drugs is a crucial determinant of viral load suppression. For the initial treatment of HIV-infected adults, a regimen with lopinavir-ritonavir combination is well tolerated and has antiviral activity superior to that of a nelfinavir-containing regimen[20]. Without complete virologic suppressed, continued virus replication in the presence of a drug can lead to the accumulation of mutations. This leads to the development of virus resistance, even to drugs with a high genetic barrier to resistance.

e) Pharmacokinetics

Although protease inhibitors have a high genetic barrier to resistance, this advantage can be lost in the setting of low serum trough concentrations. Viral mutants with low levels of resistance can continue to replicate and accumulate more mutations that lead to higher levels of resistance. Impaired drug absorption is associated with suboptimal treatment. Altered drug pharmacology including drug-drug and drug food interactions also lead to treatment failure[21].

2.5.3 Consequences of Drug Resistance

a) Viral Fittness

In general, wild-type virus replicates more efficiently (ie, is more "fit") in cell culture. It overgrows mutant strains in the absence of drug selection pressure. Drug mutations may affect viral replication efficiency or "fitness". In the setting of drug therapy, drug-resistant virus is

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selected, despite the fact that it is less fit in the absence of drug. Most drug-resistant viral variants have reduced replication fitness and have been proposed to be less pathogenic[22].

b) Cross-resistance

Sometimes a mutation develops that is unique for a particular drug. An example of this is the D30N mutation that occurs on exposure to nelfinavir. This signature mutation does not necessarily confer resistance to other protease inhibitors. Cross-resistance occurs when a single virus mutation confers resistance to more than one drug eg K103N associated with efavirenz and nevirapine. Thymidine-associated mutations (TAMs) can cause resistance to AZT, d4T, ddl, and abacavir[23]. Cross-resistance greatly limits the options of drug available for second line.

c) Hypersusceptibility

Hypersusceptibility occurs when resistance to one drug leads to increased susceptibility to another drug. For example, the M184V mutation that confers lamivudine resistance causes hypersusceptibility to zidovudine and the TAM T215Y is associated with efavirenz hypersusceptibility[10]. This characteristic enables treatment to continue in the presence of resistance to one drug owing to the mutations. This has enabled 3TC to be used in both first and second line regimens.

2.5.4 Resistance testing

This involves genotypic and phenotypic susceptibility testing of the ARVs before initiating treatment or upon development of treatment failure. Resistance testing is associated with improved survival[24]. This is because clinicians are able to select drugs that can suppress the viral replication. In treatment failure, it is the earliest indicator of drug resistance long before viremia is detected. This test is expensive and unavailable in many developing countries

2.6 Determination of Treatment Failure in Resource-Limited Settings

Optimal ART requires regular monitoring for early identification of treatment failure to prevent development of drug resistance, morbidity and mortality. Misclassification of treatment failure may result in premature switching to second-line therapy. According to the Kenya National ART Guidelines, treatment failure requires demonstration of viremia of >1000 copies/mL in a patient who has been on ART for more than 24 weeks[8]. However this test is expensive and not readily available in many centres in developing countries. Clinical and immunological monitoring are often used to assess response to treatment and predict treatment failure in resource limited settings.

When used to predict which patients have not achieved virologic suppression, clinical and immunologic criteria are associated with significant misclassification of therapeutic responses. In a study evaluating the performance of immunologic responses in predicting viral load suppression, Moore, D. M et al found that using no increase in CD4 cell counts at 6 months as a definition of treatment failure had a sensitivity of 34%, specificity of 94%, positive predictive value of 75%, and negative predictive value of 71%. At 12 months, the response values were similar[25].

In Uganda, Reynolds et al found that 68% of patients were misclassified as failing when immunologic criteria is used to determine treatment failure[26]. Kantor R et al did a study in Moi Teaching and Referral Hospital (MTRH) on misclassification of first-line antiretroviral treatment failure based on immunological monitoring of HIV infection. They found that immunological monitoring as a sole indicator of virological failure would misclassify 58% of patients who experience a 25% decrease in CD4 cell count and for 43% patients who experience a 50% decrease in CD4 cell count[27].

WHO recommends use of clinical, immunological or virological parameters to monitor patients on ART and for determination of treatment failure. In Kenya, the treatment guidelines

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recommend clinical and immunological monitoring to predict treatment failure. Viral load is only recommended to those failing on the clinical and immunologic criteria[8].

2.7 Treatment modification

Treatment Modification is defined as any alteration of 1 or more components of a patient's regimen. Substitution is change of one or two drugs within a single drug class. Switching is change between an approved first-line ART regimens to an approved second line ART regimen. In his Master of Medicine Thesis, Owour A. O found that after an average follow up of 28 months, 36.8% of patients actively on treatment had their treatment modified. The main reasons for treatment modification were toxicities, treatment failure and co-morbid conditions eg TB and pregnancy. Those who were switched to an approved second line regimen were 12.9%. All of them had first line regimen failure. Analysis of the immunologic response after treatment response showed that patients continue to have immune reconstitution. The viral response and clinical outcomes was not measured because this data was unavailable in the retrospective study and viral loads are not done routinely[4].

2.8 Outcomes of second line ART

2.8.1 Death and Loss to follow up

Patients not seen during the last 3 months are presumed to be lost to follow up. In many settings, being lost means no longer on ART[28]. Most patients who discontinue care will most likely die within one year of stopping treatment. In Johannesburg it was found that only 64.8% of patients who dropped from care were traced. Out of those traced, 48% had died, with 83% of those whose date of death was established having died with 30 days[29].

Pujades-Rodrı́guez et al studied patients switched to second line regimen in Me´decins Sans Frontie`res HIV programmes in sub-Saharan Africa, Asia, and Latin America to determine switch rates, clinical outcomes, and factors associated with survival. Median follow-up on

second-line ART was 8 months with 37% patients on treatment for more than 12 months. They found that 8% died after a median of 5 months and 5% were lost to follow up (LFU) after a median of 9 months. The probabilities of remaining alive and in care at 12 and 24 months were 0.86 and 0.77 respectively. Causes of death were found to be WHO stage 4 conditions, predominantly Karposis sarcoma, tuberculosis, wasting syndrome and other malignancies[30].

In South Africa, a study on Survival, Immune Reconstitution, and Virologic Suppression on Second-line Antiretroviral Therapy found mortality and LFU rates of 6% and 15.5% respectively after 1 year of Second line ART. The probability of remaining active in care was 0.78[31]. A Cochrane metanalysis estimated mortality at 12 months between 5.3% to 10.5% with loss to follow up at the same period ranging from 3.4% to 17%[32].

Death and LFU rates were higher in patients classified as WHO stage 4 at first-line ART initiation and in those with CD4 cell count nadir less than 50 cells/ml[30]. Other predictors of death include order age at initiation of ART, higher initial viral load and loss of weight while on ART[29].

2.8.2 Clinical Outcomes

Pujades-Rodrı´guez et al found median weight gains at 6 and 12 months after switch was 0.5 kg and 1 kg, respectively. Only 6% of patients had a BMI of less than 17 kg/m^2 1 year after the switch. After 6 months of treatment, 12.4% patients developed a WHO condition stage 3 or 4 [30]. Less opportunistic infection are found in patients who are started ART at WHO clinical stage 1 and 2 due to rapid immunologic response in this group [33].

2.8.3 Immunologic Outcomes

Studies have shown that the median CD4 cell count ranges between 184 and 258 cells/ml after 6 months of second line ART. After 12 months, this increases to between 247 and 366. Median CD4 increase is an average of 95 and 171 at 6 and 12 months, respectively. Approximately 27% of patients achieve a CD4 cell count increase of 100 cells/ml at 6 months and 46% achieve

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50 cells/ml increase. One year after switch to second line ART, 10.9% patients have a CD4 cell count of less than 50 cells/ml, 25.5% less than 100 cells/ml, and 54.5% less than 200 cells/ml[30][33][34].

In Uganda, Castelnuovo B et al prospectively studied 40 patients in second line treatment. Evaluation of CD4 count time trends in this cohort showed that after 36 months on treatment, the median CD4 count was 279 cells/ml) with a median increase of 214 cells/ml[35].

The rate of increase in CD4 cells may be slower in older patients or in those with severe immunocompromise at baseline. Viral load falling to below 500 copies/ml on the second line regimen and virologic success on the first line regimen is a predictor of good immunologic outcome[34]. Some patients may obtain viral suppression without any improvement in absolute CD4 cell counts. Risk factors for this outcome include advanced age and low nadir CD4 count. In patients who achieve and maintain viral suppression, immunologic improvement is progressive over many years[36].

2.8.4 Virologic Outcomes

Viral response after treatment failure is slower compared to treatment naive patients. Win M et al did a study on Virologic and Immunologic Outcomes of the Second-Line Regimens of Antiretroviral Therapy Among HIV-Infected Patients in Thailand. They found that after 6 months of the second-line ART 84% had HIV-1 RNA <400 copies/mL. At 12, 24, and 36 months of the second-line ART, 83%, 92%, and 90% had achieved virologic suppression respectively[33].

In South Africa, Fox M et al found that 77% of the patients started on second line ART had achieved viral suppression of <400 copies/mL after 1 year[31].

In Uganda, Castelnuovo B et al evaluated the safety and virological response to lopinavir/ritonavir containing second-line therapy after failing a first regimen up to 36 months.

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They found that by an intention-to-treat analysis, 75% of the patients were suppressed at month 12, 85% at month 24, and 82% at month 36[35].

Patients initiating a second line regimen at lower viral load and with higher CD4 cell counts are more likely to achieve undetectable viral loads[30]. Switching to second line for reasons other than non-compliance is associated with good virologic outcome [31]. Adding at least two new nucleosides to the second-line regimen is associated with better response[37]. Delayed initiation of second line ART is associated with poor virologic response[34].

2.8.5 Adherence and Toxicity outcomes

Virological success is greater among patients who have no documentation of poor adherence (<95%). After 12 months of second line therapy, 92% of patients report adherence rate >95%. At least one ART-related toxicity or laboratory abnormality is noted 62% of patients [35]. Patients with adherence rate <80% report significantly higher treatment failure rates compared to those with an adherence >95% (383 versus 176 per 1000 person years)[30]. Patients with poor adherence are five times less likely to achieve viral suppression[31].

CHAPTER 3: JUSTIFICATION OF THE STUDY

ART has significantly reduced morbidity and mortality since its introduction in 1996[12]. As ART scale up continues, more patients will require second line ART. This can be occasioned by resistance due to treatment failure and prior exposure in PMCTC or post-exposure prophylaxis (PEP). It has also been shown that there is increased development of drug resistant strains even among the ART naive patients [38].

There was no documentation of the treatment outcomes of patients on second line ART in Kenya prior to this study. The results provided important information for planning and budgeting for care and treatment services for these patients. It was important to determine retention in care so as to strengthen the meaning of these outcomes. Good clinical, immunologic and virologic outcomes of patients on follow up are put into context when assessed against the number that is retained in care over a specified period of time.

CHAPTER 4: RESEARCH QUESTION

What are the outcomes of patients switched to second line ART at Mbagathi District Hospital, comprehensive care Clinic (MDH-CCC)?

CHAPTER 5: OBJECTIVES

5.0 Broad Objective

To determine the outcomes of patients switched to second line ART at MDH-CCC.

5.1 Specific Objectives

Primary Objectives

1. To determine the clinical, immunologic and virologic outcomes of patients on second line ART.

2. To determine adherence to second line ART using pharmacy refill records.

3. To determine retention in care after switch to second line ART regimen at MDH-CCC

Secondary Objective

To correlate virologic outcomes with adherence, duration and type of first/second line regimen; WHO and CD4 count at initiation of first line, time of switch to second line ART and time of study

CHAPTER 6: METHODOLOGY

6.1 Study Design

This was a retrospective observational cohort study. Patients who had been switched to second line ART between January 2005 and March 2012 were studied to determine clinical, immunologic and virologic outcomes; and to determine levels of adherence. A subset of this population who had been switched to second line ART between January 2008 and March 2012 were studied to determine retention in care. We could not study retention in care for the period before January 2008 because there was no standardised way of keeping records of all patients switched to second line ART prior to this period. The chart below summarises the study design based on the time patients were switched to second line ART.

Figure 1: Study Design
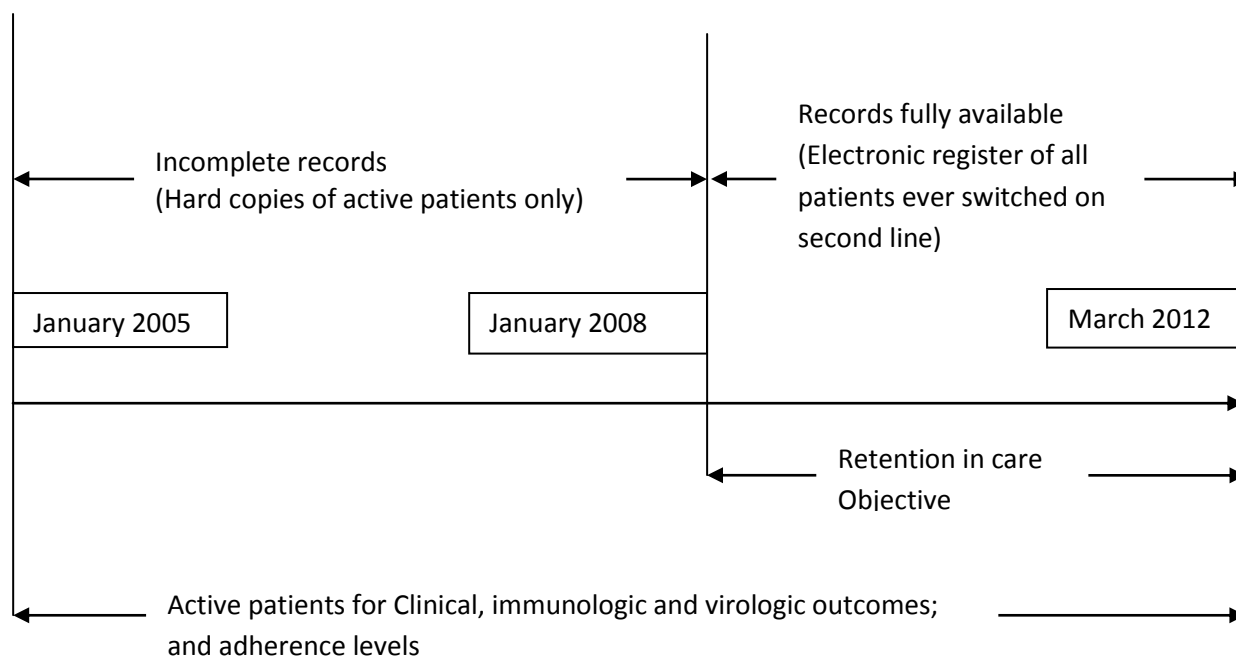
Dates indicate the time patients were switched on second line ART

6.2 Study area

The study was conducted at MDH-CCC. The CCC was started in 2003. It is donor funded and most of the cost for care and treatment is met by the donors. The cumulative number of patients as at end of September 2012 was 11,757. As at the same time, the total number of active patients on first line ART was 3,833 while those on second line ART were 344. The cumulative number of patients ever started on first line or second line cannot be determined using the information system in place. The clinic runs daily from Monday to Friday, 8am to 5pm. The patients are attended to by trained nurses, clinical officers and a medical officer. Medication is dispensed by pharmacists. The patients also receive nutrition and general counselling. The medical records are handled by qualified data clerks and records officers. The laboratory is run by laboratory technologist. The average number of patients seen per day is 120. The average number of patients seen on second line ART per day is 5.

6.3 Study population

The study population consisted of patients switched to second line ART regimen at MDH-CCC between January 2005 and March 2012

6.4 Sample Size Determination

Active patients who had been switched to second line ART between January 2005 and March 2012 were sampled to determine their clinical, immunologic and virologic outcomes. Their level of adherence was determined using pharmacy refill records.

Calculation of sample size for active patients was done using Fisher's formula as below:

$$n = \frac{Z^2 \times P\,(1-P)}{d^2}$$

n – Sample size

Z – 1.96 (95% confidence interval)

P – pooled proportion of patients achieving virologic suppression after 1 year of second line ART = 78%[32]

d – Margin of error (precision error) = ±5%

Substituting into the formula,

n = 263 (minimum sample size)

A metanalysis by Ajose O et al showed that 78% of patients on second line ART achieve virologic suppression after six months of therapy. Viral load was used to calculate the sample size because it has the lowest prevalence hence it will give the highest sample size.

A subpopulation was studied to determine retention in care. This included all patients switched to second line ART between January 2008 and March 2012.

6.5 Sampling Method

To determine clinical, immunologic and virologic outcomes and levels of adherence, consecutive sampling was done on the patients attending MDH-CCC who met the inclusion criteria until the sample size was achieved. To determine retention in care, all patients switched to second line ART between January 2008 and March 2012 were studied.

6.6 Inclusion and exclusion criteria

Inclusion criteria

1. Active patients aged more than 15 years old at the time of the study were included to determine clinical, immunologic and virologic outcomes as well as level of adherence to second line ART.

2. Patients had to have been switched to second line ART between January 2005 and March 2012.

3. Give informed consent for those over 18 years.

4. Give informed assent for those below 18 years of age and their parent or guardian to give consent for the patient to be included in further evaluation.

5. A subset of this population who had been switched to second line ART between January 2008 and March 2012 were studied to determine retention in care.

6.7 Clinical Methods, Data Collection and Analysis

To determine clinical, immunologic and virologic outcomes; and level of adherence, consecutive sampling was done from patients on second line ART attending MDH-CCC who met the inclusion criteria.

Data was collected using a predesigned questionnaire, reviewed, verified, coded and entered into a password protected Microsoft Access database.   Information on social demographic characteristics like age, gender, marital status and level of education were extracted from the files. Date of diagnosis of HIV, initiation and type of first line regimen and date of change to second line were obtained. Data on serial CD4 counts done and WHO clinical stages since the switch to second line ART were extracted from the files. This was done a day before the clinic date and any data that was incomplete was verified by the patients.

To determine clinical outcomes, history taking and physical examination were done to establish current WHO Clinical Stage. Adherence was assessed using the pharmacy refill records.

To determine retention in care, a list of all the patients switched to second line ART between January 2008 and March 2012 was obtained. An electronic database was used to confirm the patient outcomes which were recorded as active, transfer out, lost to follow up or died. Tracing was done for patients who had been lost to follow up by calling where a phone number was available.

Data was analysed using SPSS version 17.0. The gold standard for treatment response is viral load. Patients who have been on effective ART for 6 months or more should not have detectable viral load and this should be maintained irrespective of the duration of follow up. All other outcomes were analyzed without taking into account the duration of follow up. Patients who had

missing data which was required to determine an outcome of interest eg CD4 count at switch to second where not analysed for that particular outcome.

6.8 Laboratory Methods

Blood was drawn from the antecubital fossa and put in two bottles, 3mls each for CD4 count and viral load. This specimen was transported to MDH laboratory within 1 hour of collection and did not require special storage or transport.

At the laboratory, blood for CD4 count was processed immediately. Determination of CD4 count was done using an automated BD FACSCalibur® machine. The results were ready the following day. For quality assurance, the machine is calibrated every morning before running any sample. There is inter-laboratory quality control with HISS Laboratory at KEMRI CDC where comparison of tests is done on selected specimen daily. The laboratory performs monthly international quality controls which ensure results are of internationally acceptable standards.

At MDH laboratory, blood for viral load was centrifuged to separate the plasma. The plasma was stored at -20 degrees centigrade. After one week, the samples were transported in batches to KEMRI CDC laboratory in Nairobi using ice cubes to ensure the cold chain is maintained. At KEMRI laboratory, the specimen were processed immediately using ABBOTT M200 SP® for extraction and ABBOT M200 RT® for viral detection. This is an automated machine for in vitro nucleic acid processing, amplification and detection of HIV-1 RNA in plasma. The results were ready within 5 working days. For quality assurance, the machine is calibrated every time a new kit is being used for specimen analysis. Inter-laboratory quality control is done with KEMRI CDC laboratory at Busia, Kenya. The laboratory performs frequent international quality controls which ensure results are of internationally acceptable standards.

In order to ensure infection control, blood was only drawn by qualified personnel using aseptic techniques. Specimen handling, transport and processing was done using standard infection control procedures.

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6.9 Definition of Outcomes

a) Virologic Outcome

For this study, any viral load above 1000 copies/ml was defined as treatment failure. Any patient with a viral load less than 1000 copies/ml was categorised as having achieved successful virologic outcome[8].

b) Immunologic Outcome

When CD4 count fell to or below pre-second line ART levels or fell by 30% or more from peak value attained while on second line ART, this was defined as immunologic failure. If CD4 count remained persistently below 100 cells/ml after at least 12 months of effective second line ART, this was also defined as immunologic failure. Any patient who did not fulfil this criterion for immunologic failure was categorised as having achieved successful immunologic outcome[8].

c) Clinical Outcomes

A patient was defined to have clinical failure if they develop a WHO clinical stage 3 or 4 condition. Those with recurrence of previously treated opportunistic infections after at least six months of ART or downgrading of WHO clinical stage in the course of follow up were also defined to be failing clinically. Unintentional weight loss of more than 10% of baseline weight at initiation of second line ART was considered as clinical failure. Any patient who did not fulfil this criterion for clinical failure was categorised as having achieved successful clinical outcome[8].

d) Adherence

Adherence was calculated using pharmacy refill records. Patients who had picked 95% or more of their required doses of medication were categorised as having satisfactory adherence[8].

e) Active patient

An active patient was defined as any patient who had attended clinic either for review by clinician or to collect medication in the last 90 days[8].

f) Transfer out

A patient was defined as transferred out if it was documented in the medical records that the patient had been transferred to another health facility for follow up. For those lost to follow up, they were defined as transferred out if the response from the phone contacted was that the patient had been transferred out.

g) Death

A patient was defined as dead if it was documented in the medical records that the patient died. For those lost to follow up, they were defined as dead if the response from the phone contacted was that the patient died.

h) Loss to follow up (LFU)

Any patient who had not come for clinical review or to pick medication for more than 90 days and had not died or transferred out was defined as LFU[8].

6.10 Ethical Considerations

The study was undertaken after approval by the Department of Clinical Medicine and Therapeutics, University of Nairobi and the Kenyatta National Hospital/University of Nairobi Ethics and Research Review Committee. Authorization was sought from MDH administration and the CCC management.

Only those patients who gave informed consent for the study were included in for further clinical evaluation and investigations. All tests which were being done should form part of routine clinical care as part of follow up of patients on second line therapy according to the National ART Guidelines. The results of the tests were shared with the patients. Adherence intensification was recommended for those patients failing second line regimens with a repeat viral load to be done after three months. Contact tracing was done for those patients who have been lost to follow up where a phone number was available.

The data obtained from this study has been shared with MDH. A copy will be forwarded to National AIDS and STI (Sexually Transmitted Infections) Control Program (NASCOP) and The National AIDS Control Council (NACC).

CHAPTER 7: RESULTS

Patient Flow chart for the study

308 Patients switched to second line ART between January 2005 and March 2012

112 active patients switched to second line between January 2005 and December 2007 (Hard copy records of active patients available)

Switched to second line ART between January 2008 and March 2012 with complete standardised electronic records of all patients

(Studied to study retention in care) = 196

Lost to follow up = 31

Transfer out = 3

Dead = 1

Active patients = 161

273 active patients eligible for inclusion to study their clinical, immunologic and virologic outcomes; and levels of adherence

1 declined consent

(Excluded)

272 patients studied

Socio-demographic characteristics, clinical evaluation and adherence levels, blood for CD4 count and viral load

3 Invalid viral load results (Excluded, recommended repeat viral load in their next clinic visit)

269 Valid Results

(Included the in final analysis)

A total of 308 patients had been switched to second line ART between January 2005 and March 2012. There were 273 active patients who were eligible for inclusion in the clinical evaluation and laboratory testing. One patient declined consent because he was getting late for work. The number of patients evaluated was 272. At the time of analysis, 3 patients' viral load results were reported as "invalid" and a repeat was recommended. A total of 269 active patients were analysed for the clinical, immunologic and virologic outcomes and for determination of adherence levels. A subpopulation of 196 patients who had been switched to second line ART between January 2008 and match 2012 was studied to determine retention in care because they had complete records and tracer mechanisms.

The social demographic characteristics of the 269 active patients studied are summarised in table 1 below:

Baseline Characteristics of Study Subjects

Table 1: Socio-demographic Characteristics

Variable	Frequency (%)
Mean age in years (SD)	43.5 (10.3)
Range(min-max)	16.0-78.0
Gender	
Male	103 (38.3)
Female	166 (61.7)
Marital status	
Single/unmarried	65 (24.2)
Married	127 (47.2)
Divorced	2 (0.7)
Separated	36 (13.4)
Widowed	39 (14.5)
Highest level of formal education	
Primary	98 (36.4)
Secondary	137 (50.9)
Tertiary	30 (11.2)
None	4 (1.5)

The population was middle aged with a mean age of 43.5 years. Most of our patients were female (61%) with a F:M ration of 1.6:1. Majority were married (47.2%) and had some form of education (98.5%).

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Table 2: ART regimens

First line regimen	Number	Percentage
AZT/3TC/EFV	6	2.2%
AZT/3TC/NVP	24	8.9%
d4T/3TC/EFV	9	3.3%
d4T/3TC/NVP	193	71.7%
ddI/d4T/EFV	3	1.1%
TDF/3TC/EFV	3	1.1%
TDF/3TC/NVP	29	10.8%
Missing data	2	0.7%
Second line regimen		
ABC/3TC/LPV/r	60	22.3%
AZT/3TC/LPV/r	42	15.6%
d4T/3TC/LPV/r	6	2.2%
TDF/3TC/LPV/r	144	53.5%
TDF/ABC/LPV/r	17	6.3%

Most patients were on a d4T-based first line regimen (75%) while TDF-based regimen was the commonest in second line ART (59.8%). There were two patients with missing data for first line regimen.

Table 3: Follow-up data summary

	At diagnosis HIV	At initiation of ART	At first line ART failure	At switch to 2nd line ART	Status at time of study
WHO stage	n=252	n=264	n=248	n=267	n=269
1	17 (6.7)	47 (17.8)	195 (77.8)	213 (79.8)	222 (82.5)
2	30 (11.9)	28 (10.6)	19 (7.7)	20 (7.5)	29 (10.8)
3	179 (71.0)	167 (63.3)	26 (10.5)	28 (10.5)	12 (4.5)
4	26 (10.3)	22 (8.3)	10 (4.0)	6 (2.2)	6 (2.2)
Weight (Kg)	n=244	n=261	n=247	n=268	n=269
Mean (SD)	57.9 (14.0)	58.3 (13.5)	62.9 (12.8)	62.3 (12.6)	65.9 (14.2)
CD4 count (cells/ml)	n=206	n=254	n=231	n=243	n=269
Median (IQR)	58 (15-66)	61 (17-145)	133 (73-200)	133 (64-228)	408 (243-576)
Viral load (copies/ml)	n=3	n=8	n=217	n=206	n=269
Median (IQR)	66899 (5715-291000)	139450 (7250-553668)	46651 (11945-163217)	50193 (13023-168609)	0 (0-150)

At initiation of first line ART, majority of patients had advanced HIV disease with 71.6% in WHO clinical stage 3 and 4. The median CD4 count at the same period was 61 cells/ml. Only 8

patients had viral loads done at initiation of ART. The mean weight was 58.3kg. At the time of switch to second line, most patients (87.3%) were in WHO clinical stage 1 and 2 with a mean weight of 62.3kg and median CD4 count of 133 cells/ml. There were 217(80.7%) patients who had virologic confirmation of treatment failure before switch to second line. The number of patients who had a recent viral load at the time of switch to second line ART was 206(76.5%). Recent viral load was defined by having a viral load done within the last six months prior to switch to second line ART. There were 11 patients who had delay to switch to second line ART of more than six months after the virologic diagnosis of treatment failure. They were considered not to have a recent viral load at the time of switch to second line ART. The median viral load at the time of switch to second line ART was 50,193 copies/ml.

Table 4: Reasons for change to second line regimen

Variable	Frequency, n (%)
Clinical Failure	32 (11.9)
Immunologic Failure	224 (83.3)
Virologic Failure	215 (79.9)
Other reasons accompanying clinical, immunologic and/or virologic failure	
Pregnancy	1 (0.4)
Gynecomastia	1 (0.4)
Hepatotoxicity	4 (1.4)
Hyperlactimia	1 (0.4)
Lactic acidosis	3 (1.1)
Lipodistrophy	48 (17.9)
Polyneuropathy	1 (0.4)
Severe Rash	7 (2.6)

Most patients had more than one indication for switch to second line ART. There were 48 (17.9%) patients with documented lipodystrophy at the time of switch to second line ART. All had diagnosed treatment failure using clinical, immunologic or virologic parameters. There was one client who was pregnant and two with lactic acidosis and who were switched to second line therapy without diagnosis of treatment failure in routine clinical and immunologic monitoring. However when viral load was done they were found to have virologic failure. There were 13

patients who had random viral loads done and were found to have virologic failure without immunologic or clinical failure.

Clinical, Immunologic and Virologic Outcomes of Second Line ART

Table 5: Comparison of WHO stage, CD4 count and viral load at switch to 2nd line and time of study

	At initiation of 2nd line ART	Time of study	P value
Mean weight in Kg (SD)	61.8 (13.4)	66.7 (15.2)	<0.001
WHO clinical stage 1 2 3 4	213 (79.8) 20 (7.5) 28 (10.5) 6 (2.2)	220 (82.4) 29 (10.9) 12 (4.5) 6 (2.2)	0.075
Median CD4 count cells/ml(IQR)	133 (64-228)	408 (244-571)	<0.001
Median viral load copies/ml (IQR)	15133 (59000-143000)	0 (0-150)	<0.001
Viral load (copies per ml) >=1000 (%) <1000 (%)	206 (99) 2 (1)	34 (11.6) 235 (88.4)	<0.001

To answer the first primary objective, WHO clinical stage, CD4 count and viral load of study subjects were compared between the time of switch to second line ART and the time of study. There was good response to second line ART with 93.3% of the patients being in WHO stage 1 and 2 at the time of the study. The mean weight increased to 65.9kg. There were 18(6.7%) patients with BMI less than 18 Kg/m^2. The median CD4 count rose to 408 (IQR = 243-576) cells per ml while the median viral load was less than the low detectable levels (IQR= 0-150 copies per ml). Weight increase, CD4 rise and virologic suppression as a measure of response to second line were statistically significant. We found that 3.3 % of patients had CD4 count below 100 while 15.2% were below 200 at the time of study.

The median duration of 1st line was 38 months (IQR = 25-57). The median delay to switch to 2nd line was 84 days (IQR = 35-168) while the median duration of second line ART was 43 months

(IQR = 23-68) with a range of 6-99 months. Delay to switch to second line ART is the period between diagnosis of ART failure and initiation of second line regimen.

Table 6: Clinical conditions of study subjects at the time of study

Condition	Frequency, n (%)
Asymptomatic	223 (82.9)
Mucocutaneous manifestations	26 (9.7)
URTI	2 (0.7)
Candidiasis	1 (0.4)
PTB	10 (3.7)
Severe Bacterial Infections	1 (0.4)
Cryptococcal Meningitis	1 (0.4)
Chronic Orolabial ulcers	1 (0.4)
Kaposi's Sarcoma	3 (1.1)
PML	1 (0.4)

Majority (82.9%) of the patients were asymptomatic at the time of the study. There were 26(9.7%) patients with minor mucocutaneous manifestations while 10 (3.7%) had pulmonary TB. Other conditions were as shown in the table 6.

Table 7: Summary of outcomes of study subjects

Outcome	Frequency, n (%)
Successful Clinical Outcome (n=269)	
Yes	251 (93.3)
No	18 (6.7)
Successful Immunologic Outcome (n=243)	
Yes	218 (89.7)
No	25 (10.3)
Successful Virologic Outcome (n=269)	
Yes	235 (87.6)
No	34 (12.4)

There were 251 (93.3%) patients with successful clinical outcomes while 89.7% had successful immunologic outcome. Some study participants did not have CD4 counts for specified periods as defined by the study and they were excluded from analysis for this particular outcome. The number of patients with viral load less than 1000 copies per ml was 235 corresponding to a virologic treatment success of 87.6%. Out of the patients with virologic failure, only 4 (11.8%) had both virologic and immunologic failure. Another 4 (11.8%) had both clinical and virologic

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failure while only 1 had clinical, immunologic and virologic failure. The range of viral load for the failing patients was between 1066 and 567,778 with a median 37,282 (IQR 20024-212640).

Adherence levels using pharmacy refill record

Table 8: Adherence Levels

n =269	
≥95% (Satisfactory)	264 (98.1)
<95% (Unsatisfactory)	5 (1.9)

To answer the second primary objective, levels of adherence were analysed using pharmacy refill records. There were 264 (98.1%) patients with satisfactory adherence (≥95%). Out of the five patients with unsatisfactory adherence (<95%), only 2 had virologic failure. This was 5.9% of the 34 patients who had virologic failure.

Determination of retention in care

Table 10: Retention in care of 196 study subjects with 4 year follow up

Status at time of study	Frequency, n (%)
Active	161 (82.1)
Dead	1 (0.5)
Lost to follow up	31 (15.8)
Transferred out	3 (1.5)

To answer the third primary objective, 196 patients who had been switched to second line ART between January 2008 and March 2012 were studied to determine retention in care. Out of this, 161 patients were active in care at the time of the study reflecting retention in care rate of 82.1% after a mean duration of follow up of 35.4 months. This means that the clinical, immunologic and virologic outcomes and adherence levels described above represent majority of the patients ever switched to second line ART. At the time of the study, 31 patients (15.8%) had been LFU

while one patient was documented as dead. The mean duration to LFU was 13.5 months. There were 3(1.5%) patients who had been transferred out.

Figure 1: Kaplan Mayer curve showing the probability or remaining in care after switch to second line ART
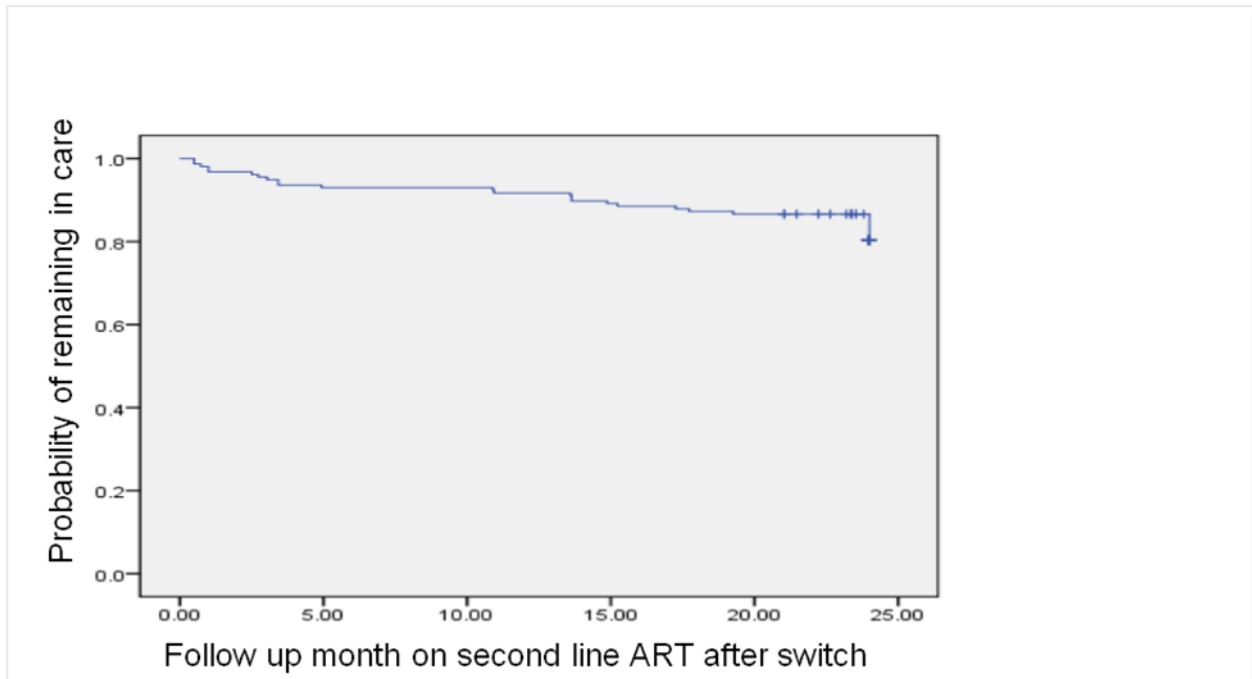
We drew a Kaplan Mayer curve to determine the probability of remaining active in care after switch to second line ART. We found that approximately 90% of patients were likely to be active in care after a mean duration of 24 months of second line ART.

Correlation of virologic outcomes with various study variables

Table 9: Comparison of various variables by virologic outcomes

Variable	Virologic failure	Viral suppression	P value
Median CD4 count at initiation of 1st line in cells/ml (IQR)	55 (16-141)	125 (63-261)	0.077
Median CD4 count at switch to 2nd line in cells/ml (IQR)	129 (57-215)	188 (20-311)	0.734
Median current CD4 in cells/ml (IQR)	409 (257-586)	527 (346-740)	0.197
Median change in weight while on second line ART in (IQR)	2.5 (0.0-8.5)	3.0 (-4.0-10.0)	0.963
Median delay to initiation of 2nd line in days (IQR)	84.0 (38.0-189.0)	63.0 (28.0-91.0)	0.153
Median duration of 1st line in months (IQR)	38.0 (26.0-55.0)	32.0 (24.0-60.0)	0.712
Median duration of 2nd line in months (IQR)	52(28-64)	42(24-66)	0.777
Adherence Levels >=95% Satisfactory <95% Unsatisfactory	32 (94.2%) 2 (5.9%)	232(98.7%) 3 (1.3%)	0.325

To answer the secondary objective, we looked for associations of different parameters and virologic outcomes. We compared virologic failure and adherence, first and second line regimens, CD4 cell count and WHO clinical stage at different times of patient follow up and none of them achieved statistical significance. There was no association between virologic failure with duration of first or second line regimen as well as the duration of delay to initiation of second line regimen.

Discussion

We found 87.6% of study patients had virologic suppression of less than 1000 copies per ml after a mean duration of 43 months of second line ART. Other studies have reported virologic suppression ranging between 62-90% after follow up for 36 months on second line ART[32][33][35]. This study showed that the patients with virologic failure had longer duration of follow up, however this was not statistically significant. Our good virologic suppression can be attributed to the higher levels of adherence since satisfactory adherence is associated with favourable treatment outcomes[31].

According to the Kenya National ART treatment guidelines, immunologic monitoring is used to monitor HIV patients with targeted viral load being performed to confirm treatment failure[8]. Studies have shown that there is weak correlation between immunologic and virologic failure[27][39]. We showed that when immunologic criteria were used to monitor patients on second line ART, it failed to identify 30 (88.2%) of the 34 patients who had virologic failure.

The consequences of remaining on a virologically-failing regimen include progression to immunologic and clinical failure. With increasing duration of viraemia, accumulation of drug resistance mutations occurs. These patients' care is more costly because they will require specialized tests like resistance testing and expensive alternative antiretroviral drugs like raltegravir and maraviroc which are not readily available. They are also at risk of transmitting drug resistant strains to their sexual partners[18]. In Kenya, it is only at KNH where routine viral load testing for monitoring patients on second line ART is done. Studies have shown that baseline and serial elevation in the total CD8 count as well as an increase in CD8 counts after initiation of ART are associated with increased risk of virologic failure[40]. Both CD8 counts and CD4/CD8 ratios can be explored further in studies as an affordable predictor of virologic failure.

Despite the good virologic response, the proportion of those with virologic failure cannot be ignored. It is important to explore the reasons for failure in these patients. Studies have

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associated virologic failure with accumulation of resistant mutations and drug pharmacokinetics[19 21]. Majority of our patients were on d4T or AZT-based first line regimen as per the guidelines then. This may be associated with accumulation of TAMs that confer resistance to TDF and ABC which are the choices for second line in local ART public health programmes. The guidelines have since been revised and now TDF is preferred because the mutations associated with it preserve future treatment options. Our finding can be generalised in the country because the care and treatment offered in MDH-CCC can be replicated in many health facilities. This would translate to approximately 1500 patients failing second line ART nationally over approximately a four year period of second line ART.

We found adherence levels of 98% comparable to 97% in the study done by Castelnuovo B et al[35]. They used self-report to calculate adherence whereas we used pharmacy refill records in this study. Both methods are validated for assessing adherence, however with drawbacks. Use of home visits, participation in support groups, unannounced pill counts by primary care provider and having counselling sessions by a pharmacist have been shown to strengthen adherence[41], but these were not included in this study nor are they established standards of care in this clinic. We did not find statistically significant association between satisfactory adherence and virologic suppression. This could be due to the intensive adherence counselling done for all patients on ART as shown by the high levels of adherence (98%). Virologic failure in our patient population could thus be attributed to other factors eg drug resistance mutations.

We found a median CD increase of 275 cells/ml and only 9 patients had CD4 counts below 100 cells/ml. The overall immunologic response was better compared to other studies on second line ART[30 34]. This could be attributed to longer duration of follow up. It has been shown that there is progressive immunologic improvement over many years of effective ART[36]. The 9 patients with CD4 counts persistently below 100 cells/ml were found to have adequate virologic suppression.

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This finding is common among patients with low nadir CD4 count at initiation of first line ART[36].

We found 93.3% of patients with clinical treatment success. Weight gain and BMI were comparable to the study done in MSF programs in resource limited setting[30]. Clinical failure lags behind immunologic and virologic failure. MDH-CCC uses immunologic monitoring but does virologic confirmation of treatment failure. Majority of patients had not exhibited clinical failure at the time of switch to second line ART. They remained in WHO clinical stage 1 and 2 over the duration of second line therapy.

These clinical, immunologic and virologic outcomes are a good representative of the patients ever switched to second line ART since majority (82%) remained active in care. Data from NASCOP estimates the average retention in care after 24 months of follow up from initiation of ART at 72%[1]. The retention in care observed within the period when records were fully available of over four years may be projected to be overall proportion of patients retained in care from 2005. This was comparable to Pujades-Rodríguez et al who found the probabilities of remaining alive and in care at 12 and 24 months of second line ART were 0.86 and 0.77 respectively although over shorter durations of second line ART[30].

Achieng L et al found retention in care rate of 84.3% after 12 months of follow up at Kijabe Mission Hospital. However their study was for patients on first line and their duration of follow up was shorter compared to 4 years in our study[41]. MDH-CCC is a mature clinic with most requirements for chronic care being offered eg adherence counselling, psychosocial support, peer education, nutrition counselling, defaulter tracing and home visits. This could contribute to the good retention in care after a longer duration of follow up. At the time of the study, 31 patients (15.8%) had been lost to follow up while one patient was documented as dead. A Cochrane meta-analysis estimated mortality at 12 months between 5.3% to 10.5% with loss to follow up at the same period ranging from 3.4% to 17%[32]. Majority of the patients who discontinue care die

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within 1 year of stopping treatment[29]. There is need to strengthen defaulter tracing of patients LFU so has to link them to care and treatment services at centres proximal to them.

Our results showed more favourable outcomes compared to other studies done to determine outcomes of second line ART. All the studies used for comparison were prospective while our study was retrospective. This could have introduced a survival bias. Our study was done in a mature clinic with well established components of chronic care. Comparison studies were done when HIV/AIDS services were being set up and lacked good chronic care facilities.

Conclusion

We showed that second line ART is associated with good clinical, immunologic and virologic outcomes in MDH-CCC as expected. We found that most patients had satisfactory adherence to their therapies. Retention in care after switch to second line ART was high with 82% being active in care after a mean duration 35 months.

Recommendations

- Virologic monitoring should be made part of routine follow up of patients on second line ART.

- It is apparent that 34 (12.4%) patients had virologic failure after a median duration of 52 months of second line ART. This is relatively a short period for patients anticipated to be on lifelong treatment. There is need for treatment programs to plan for future treatment options for these patients failing second line ART.

CHAPTER 8: STUDY LIMITATIONS

1. We had missing data on the patients ever switched to second line ART since 2005. This prevented us from studying retention in care over a longer duration of follow up before 2008.

2. Phone response was used to contact those lost to follow up. This was depended on accurate updated documentation of phone contacts. None of the patients who were lost to follow up could be traced on documented phone contacts.

3. Retrospective review of clinical data for WHO clinical stages generated by multiple care providers.

REFERENCES

1. Kenya HIV Drug Resistance Country Report. 2011.

2. Minimum Package of Care in HIV Services Provision, Ministry of Medical Services/NASCOP. 2011;(October).

3. Global HIV/AIDS Response, Progress Report. 2011.

4. Owuor, A. Modification of Antiretroviral Therapy in HIV-infected Patients Between 2005-2011 at The KNH Comprehensive Care Clinic. 2012.

5. Fischl, M.A., Richman, D.D., Grieco M.H., *et al*. The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-related Complex. A double-blind, placebo-controlled trial. *The New England Journal of Medicine*. 1987;317(4):185–191.

6. Kenya Demographic Health Survey. 2008.

7. WHO Adult and Adolescents ART Recommendations. 2009;(November).

8. Guidelines for Antiretroviral Therapy in Kenya, 4th Edition. 2011;(November).

9. Stephan, C., Dauer, B., Bickel, M., *et al*. Intensification of a Failing Regimen with Zidovudine may Cause Sustained Virologic Suppression in the Presence of Resensitising Mutations Including K65R. *The Journal of infection*. 2010;61(4):346–50

10. Larder, B.A., Kemp, S.D., Harrigan, P.R. Potential Mechanism for Sustained Antiretroviral Efficacy of AZT-3TC Combination Therapy. *Science*. 1995;269(5224):696–699.

11. Torti, C., Pozniak, A., Nelson, M., *et al*. Distribution of K103N and/or Y181C HIV-1 Mutations by Exposure to Zidovudine and Non-nucleoside Reverse Transcriptase Inhibitors. *The Journal of antimicrobial chemotherapy*. 2001;48(1):113–6.

12. Lee, L.M., Karon, J.M., Selik, R., *et al*. Survival after AIDS Diagnosis in Adolescents and Adults During the Treatment Era, United States, 1984-1997. *Jama The Journal Of The American Medical Association*. 2001;285(10):1308–1315.

13. Le Moing, V., Thiébaut, R., Chêne, G., *et al*. Predictors of Long-term Increase in CD4(+) Cell Counts in Human Immunodeficiency Virus-infected Patients Receiving a Protease Inhibitor-containing Antiretroviral Regimen. *The Journal of Infectious Diseases*. 2002;181(5):471–480.

14. Maartens, G., Boulle, A.CD4 T-Cell Responses to Combination Antiretroviral Therapy. *Lance*. 2007;370(9585):366–368.

15. Sufka, S.A., Ferrari, G., Gryszowka, V.E., *et al*. Prolonged CD4+ Cell/Virus Load Discordance During Treatment With Protease Inhibitor-based Highly Active Antiretroviral Therapy: Immune Response and Viral Control. *The Journal of Infectious Diseases*. 2003;187(7):1027–1037.

16. Deeks, S.G., Barbour, J.D., Grant, R.M., *et al*. Duration and Predictors of CD4 T-cell Gains in Patients who Continue Combination Therapy Despite Detectable Plasma Viremia. *AIDS*. 2002;16(2):201–207.

17. Hammer, S.M., Eron, J.J., Reiss, P., *et al*. Antiretroviral Treatment of Adult HIV 1nfection: 2008 Recommendations of the International AIDS Society-USA Panel. *Jama The Journal Of The American Medical Association*. 2008;300(5):555–570.

18. Cohen, M.S., McCauley, M., Gamble, T.R. HIV Treatment as Prevention and HPTN 052. *Current opinion in HIV and AIDS*. 2012;7(2):99–105.

19. Paterson, D.L., Swindells, S., Mohr, J., *et al*. Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection. *Annals of Internal Medicine*. 2000;133(1):21–30.

20. Hospital, F.T., Laboratories, A., Park, A., *et al*. Lopinavir – Ritonavir Versus Nelfinavir for The Initial Treatment of HIV Infection. *The New England Journal of Medicine*. 2002;346(26):2039–2046.

21. Schouten, J.T. HIV Drug Resistance and the Other Causes of Treatment Failure. *Step Perspective*. 1997;9(3):5–8.

22. Deeks, S.G., Hoh, R., Neilands, T.B., *et al*. Interruption of Treatment with Individual Therapeutic Drug Classes in Adults with Multidrug-resistant HIV-1 Infection. *The Journal of Infectious Diseases*. 2005;192(9):1537–1544.

23. Bacheler, L., Jeffrey, S., Hanna, G.*, et al*. Genotypic Correlates of Phenotypic Resistance to Efavirenz in Virus Isolates from Patients Failing Nonnucleoside Reverse Transcriptase Inhibitor Therapy. *Journal of Virology*. 2001;75(11):4999–5008.

24. Baxter, J.D., Mayers, D.L., Wentworth, D.N., *et al*. A Randomized Study of Antiretroviral Management Based on Plasma Genotypic Antiretroviral Resistance Testing in Patients Failing Therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS*. 2000;14(9):F83–F93.

25. Moore, D.M., Mermin, J., Awor, A., *et al*. Performance of Immunologic Responses in Predicting Viral Load Suppression: Implications for Monitoring Patients in Resource-limited Settings. *Journal of Acquired Immune Deficiency Syndromes*. 2006;43(4):436–439.

26. Reynolds, S.J., Nakigozi, G., Newell, K., *et al*. Failure of Immunologic Criteria to Appropriately Identify Antiretroviral Treatment Failure in Uganda. *AIDS*. 2009;23(6):697–700.

27. Kantor, R., Diero, L., Delong, A., *et al*. Misclassification of First-line Antiretroviral Treatment Failure based on Immunological Monitoring of HIV Infection in Resource-limited Settings. *Clinical Infectious Diseases*. 2009;49(3):454–462.

28. The President's Emergency Plan for AIDS Relief, Indicators Reference Guide. 2007.

29. Dalal, R.P., Macphail, C., Mqhayi, M., *et al*. Characteristics and Outcomes of Adult Patients Lost to Follow-up at an Antiretroviral Treatment Clinic in Johannesburg, South Africa. *Journal of Acquired Immune Deficiency Syndromes*. 2008;47(1):101–107.

30. Brien, D.O., Humblet, P., Pujades-rodrı, M., *et al*. Second-line Antiretroviral Therapy in Resource-limited Settings:The Experience of Me´decins Sans Frontie`res. *Lippincott Williams & Wilkins*. 2008;22(11):1305-1315.

31. Fox, M.P., Ive, P., Long, L., *et al*. High Rates of Survival, Immune Reconstitution, and Virologic Suppression on Second-line Antiretroviral Therapy in South Africa. *Journal of Acquired Immune Deficiency Syndromes*. 2010;53(4):500–506.

32. Ajose, O., Mookerjee, S., Mills, E.J., *et al*. Treatment Outcomes of Patients on Second-line Antiretroviral Therapy in Resource-limited Settings : a Systematic Review and Meta-analysis. *AIDS*. 2012:26(8):929–938.

33. Win, M.M., Maek-A-Nantawat, W., Phonrat, B., *at al*. Virologic and Immunologic Outcomes of the Second-Line Regimens of Antiretroviral Therapy Among HIV-Infected Patients in Thailand. *Journal of the International Association of Physicians in AIDS Care (Chicago, Ill. : 2002)*. 2011;10(1):57–63.

34. Mocroft. A,, Phillips, A.N., Miller, V., *et al*. The Use of and Response to Second-line Protease Inhibitor Regimens: Results From the EuroSIDA Study. *AIDS*. 2001;15(2):201–9.

35. Castelnuovo, B., John, L., Lutwama, F., *et al*. Three-year Outcome Data of Second-line Antiretroviral Therapy in Ugandan Adults: Good Virological Response but High Rate of Toxicity. *Journal of the International Association of Physicians in AIDS Care (Chicago, Ill. : 2002)*. 2009;8(1):52–9.

36. Mocroft. A., Phillips, A.N., Gatell, J., *et al*. Normalisation of CD4 Counts in Patients with HIV-1 Infection and Maximum Virological Suppression who are Taking Combination Antiretroviral Therapy: an Observational Cohort Study. *Lance*. 2007;370(9585):407–13.

37. Levison, J.H., Orrell, C., Losina, E., *et al*. Early Outcomes and the Virologic Impact of Delayed treatment Switching on Second-line Therapy in an Antiretroviral Roll-out Program in South Africa. *Antivir Ther*. 2012;16(6):853–861.

38. Gupta R.K., Jordan, MR., Sultan, B.J., *et al*. Global Trends in Antiretroviral Resistance in Treatment-naive Individuals with HIV after Rollout of Antiretroviral Treatment in Resource-limited Settings : A Global Collaborative Study and Meta-regression Analysis. *The Lancet*. 2012;6736(12):1–9.

39. Schoffelen, A.F., Wensing, A.M.J., Tempelman, H. A., *et al*. Sustained Virological Response on Second-Line Antiretroviral Therapy following Virological Failure in HIV-Infected Patients in Rural South Africa. *PloS one*. 2013;8(3):e58526.

40. Krantz, E.M., Hullsiek, K.H., Okulicz, J.F., *et al*. Elevated CD8 Counts During HAART are Associated with HIV Virologic Treatment Failure. *J Acquir Immune Defic Syndr*. 2012;57(5):396–403.

41. Achieng L, Musangi H, Ong S, et al. An Observational Cohort Comparison of Facilitators of Retention in Care and Adherence to Anti-Retroviral Therapy at an HIV Treatment Center in Kenya. *PloS one*. 2012;7(3):e32727.

APPENDIX I: DATA ABSTRACTION TOOL

CCC Number ---------------------------   Study number ----------------------

1. Age: ------------------

2. Gender: Male------   Female --------

3. Marital status(Tick one):

    Single ----   Married ----   Divorced ----   Separated ---- Widowed ----

4. Level of education (tick one):

    Primary------   Secondary------   Tertiary-----   None -----

5. Reason for Change to second line

    a. Treatment failure: Clinical ------- Immulogic ------- Virologic -------

    b. Toxicity and Drug(s) ---

    c. Co-morbidities: TB   Pregancy   Other -------------------------------

    d. Other Reasons --

6. Duration of First line (months)   ----------------------------------

7. Duration from diagnosis of treatment failure to change to second line (months)

                                                   ----

8. Duration of second line (months)   ----------------------------------

OUTCOMES

1. Active   -----------------

2. Died   -----------------

3. Transfer   -----------------

4. Lost to follow up   -------------

   Traced (Tick as appropriate)?

   a. No -----

   b. Yes -----

   c. If yes outcome of tracing

      i. Transferred

      ii. Not in care

      iii. Died

      iv. Other outcomes (specify) ---

CLINICAL EVALUATION

Presenting Complaint

Current Medical Problem

Condition/Who Stage	Tick if present
Clinical Stage 1	
1. Asymptomatic	
2. Persistent generalized lymphadenopathy (PGL)	
Clinical Stage 2	
1. Moderate unexplained weight loss (<10% of presumed or measured body weight)	
2.Minor mucocutaneous manifestations (seborrheic dermatitis, popular pruritic eruptions, fungal nail infections, recurrent oral ulcerations, angular cheilitis)	
3. Herpes zoster	
4. Recurrent upper respiratory tract infections (sinusitis, tonsillitis, bronchitis, otitis media, pharyngitis)	
Clinical Stage 3	
1. Unexplained severe weight loss (over 10% of presumed or measured body weight)	
2. Unexplained chronic diarrhoea for longer than one month	
3. Unexplained persistent fever (intermittent or constant for longer than one month)	
4. Persistent oral candidiasis	
5. Oral hairy leukoplakia	
6. Pulmonary tuberculosis	
7. Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)	
8. Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis	
9. Unexplained anaemia (below 8 g/dl), neutropenia (below 0.5 x 109/l) and/or chronic thrombocytopenia (below 50 x 10^9 /l)	
Clinical Stage 4 Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations:	
1. HIV wasting syndrome	
2. Pneumocystis jiroveci pneumonia (PCP)	

3. Recurrent severe bacterial pneumonia (≥ 2 episodes within 1 year)	
4. Cryptococcal meningitis	
5. Toxoplasmosis of the brain	
6. Chronic orolabial, genital or ano-rectal herpes simplex infection for >1 month	
7. Kaposi sarcoma (KS)	
8. HIV encephalopathy	
9. Extra pulmonary tuberculosis (EPTB)	
10. Cryptosporidiosis, with diarrhoea >1 month	
11. Isosporiasis	
12. Cryptococcosis (extra pulmonary)	
13. Disseminated non-tuberculous mycobacterial infection	
14. Cytomegalovirus (CMV) retinitis or infection of the organs (other than liver, spleen, or lymph nodes)	
15. Progressive multifocal leucoencephalopathy (PML)	
16. Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis)	
17. Candidiasis of the oesophagus or airways	
18. Non-typhoid salmonella (NTS) septicaemia	
19. Lymphoma cerebral or B cell Non Hodgkin's Lymphoma	
20. Invasive cervical cancer	
21. Visceral leishmaniasis	
22. Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy.	

Physical Examination

Temp...........^{o}C   PR................../min   RR.............../min   BP................mm/Hg

Weight.............Kg   Height............ m   BMI...............Kg/m^{2}

Lymph node   --

Skin and nails --

Mouth ---

ENT ---

CNS --

Lungs ---

Cardiovascular System ---

Gastrointestinal System ---

Genitourinary System --

Musculoskeletal --

Medications (Circle)

      Cotrimoxazole multivitamin   fluconazole   dapsone

      Others (state) ---

Clinical Diagnosis

WHO Clinical Stage   ------------------------------------

CD4   Count   ------------------------------------

Viral load   (copies per ml)   ------------------------------------

Other investigation done

Data Collection Form I

Parameters	Date	Weight in KG	BMI	WHO Stage	CD4 Count (cell/ml)	Viral Load (copies per ml)
HIV Diagnosis						
Initiation of ART						
Treatment Failure Diagnosed						
Change to Second line						
Date/Value of parameter /duration of Second line ART in months — First visit — Date						
First visit — Value						
First visit — Duration						
2nd Visit — Date						
2nd Visit — Value						
2nd Visit — Duration						
3rd visit — Date						
3rd visit — Value						
3rd visit — Duration						
4th Visit — Date						
4th Visit — Value						
4th Visit — Duration						
5th Visit — Date						
5th Visit — Value						
5th Visit — Duration						

Data Collection Form II

Date/ Value of parameter **/duration** of Second line ART in months

Visit Number	Parameters	Weight in KG	BMI	WHO Stage	CD4 Count (cell/ml)	Viral Load (copies per ml)
	Date					
	Value					
	Duration					
	Date					
	Value					
	Duration					
	Date					
	Value					
	Duration					
	Date					
	Value					
	Duration					
	Date					
	Value					
	Duration					
	Date					
	Value					
	Duration					
	Date					
	Value					
	Duration					

APPENDIX II: PATIENT CONSENT EXPLANATION FORM

Introduction

I am a postgraduate student currently doing a masters' degree in Internal medicine at the University of Nairobi. I am conducting my research project for which I request your participation.

Patients are initiated on first line drugs and when they are not responding, they are evaluated to find out the cause of non-response. They are changed to second line drugs if they are adherent and the cause of non response is called treatment failure. We do not know the outcomes of patients on second line therapy in Kenya.

REASONS FOR DOING THE STUDY

This study will assess the outcome of patients on second line antiretrovirals. This is important because there is any increase in the number of people on second line antiretroviral treatment due to scale up of ART services. Information from this study will assist in budgeting for HIV care and treatment services. It will also assist in planning for patients who fail second line therapy.

BENEFITS OF PARTICIPATION

The immediate benefits of this study will be to give information on success of treatment with second line therapy. Participants will have clinical examination and laboratory tests done to determine the response of the drugs to the virus and the immunity.

RISKS OF PARTICIPATION

All tests being done form part of routine clinical care. There are minimal risks involved in clinical assessment and laboratory tests to determine response to second line antiretrovirals. You may feel a slight discomfort from the needle prick while blood is being drawn. This is no different from that felt while drawing blood for other tests.

The medical records and data abstracted for this study will only be accessible to authorised persons. This will minimise accidental disclosure to any unauthorised personnel.

If you consent for the study, you will be expected to give information about you self and the illness you have. You will expect to be examined and blood drawn by a qualified clinician for

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CD4 count and viral load. A copy of the results will be put in your file. It will be available to assess how you are responding to treatment.

CONSENT TO PARTICIPATION

Participation in this study is of your own free will. You will not be forced to participate, and you have a choice of withdrawing from the study at any point. Standard treatment will be offered to all patients, whether or not they choose to participate in this study.

CONTACTS

For further information, you may contact any of the following:

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P.O Box 4714 – 00100 NAIROBI.

Tel 0721-431150

2. Dr. Loice Achieng (Supervisor)

P. O Box 19676 - 00202 Kenyatta National Hospital.

Tel 0722-576984

3. Kenyatta National Hospital/University of Nairobi Ethics and Research Review Committee,

P.O Box 20723 NAIROBI.

Tel 020-726300

KUHUSU IDHINI

Mimi ni mwanafunzi katika chuo kikuu cha Nairobi. Ninatarajia kufanya utafiti kuhusu madawa ya kupunguza makali ya ukimwi na ningependa wewe uhusike.

Mtu anayeungua ukimwi huanzishwa madawa ya kiwango cha kwanza. Wakati madawa haya yanaposhindwa nguvu mgonjwa hupewa madawa ya kiwango cha pili. Haijulikani jinsi wagonjwa wanaopewa madawa ya kiwango cha pili huendelea.

SABABU ZA KUFANYA UTAFITI

Utafiti huu utasaidia kujua jinsi watu wanaopewa madawa ya kiwango cha pili wanavyoendelea. Itasaidia kuweka mipango ya kuendelea kutoa matibabu haya.

MANUFAA YA KUHUSIKA

Manufaa ya utafiti huu ni kujua jinsi madawa yanavyofanya kazi kwa mwili yako. Ukipimwa na upatikane na ugonjwa utatibiwa. Ikiwa itapatikana kuwa dawa haifanyi kazi utafunzwa jinsi ya kuitumia dawa vilivyo.

MADHARA YA KUHUSIKA

Vipimo vyote ni baadhi ya mahitaji ya kuhudunia wagonjwa wanapewa madawa ya kupuguza makali ya ukimwi. Hakuna madhara yatakayotokana na kuhusika katika utafiti huu. Unaweza kusikia uchungu kidogo kutokana na sindano wakati wa kutolewa damu. Uchungu huu ni sawa na ule unaosikika wakati unapotolewa damu kwa vipimo vingine.

IDHINI KWA KUHUSIKA

Kuhusika kwako katika utafiti huu ni kwa hiari yako. Unaweza kujiondoa kwa utafiti kwa wakati wowote kabla au baada ya utafiti kuanza. Matibabu yanayostahili yatapewa kwa watu wote na wale watakaokataa kuhusika hawatabaguliwa kwa njia yoyote.

Makala ya matibabu pamoja na vipimo zitakazofanywa kwa utafiti zitawekwa vizuri na kuhakikisha kwamba hakuna mtu atakaweza kuzipata bila idhini.

Ukikubali kuhusika kwa utafiti huu, utapaswa kupeana habari kuhusu wewe binafsi na pia kuhusu madhara uliyonayo. Utapaswa kupimwa kimwili na kutolewa ndamu ya kupima kiwango cha kinga mwilini na virusi vilivyo katika ndamu yako. Majibu ya vipimo yakitoka utapewa pamoja na daktari wako na yatatumika kwa matibabu.

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MAWASILIANO

Ukiwa na maswali yoyote ya ziada, unaweza kuwasiliana na watafiti.

1.   Dkt. Kiio S. Ndolo (mtafiti mkuu)

        SLP 4714 – 00100 NAIROBI

        Nambari ya simu: 0721-431150

2.   Dr. Loice Achieng (msimamizi)

        SLP 19676 – 00202 Hospitali Kuu ya Kenyatta

        Simu: 0722-576984

3.   Kamati ya Maadili ya Hospitali ya Kenyatta na Chuo kikuu cha Nairobi

        SLP 20723 NAIROBI

        Simu: 020-726300

APPENDIX III: PATIENT CONSENT FORM

I, the undersigned have read and fully understood the explanation given to me regarding this study. All my questions have been answered satisfactorily by the investigators. I hereby consent to my/my child's participation in this study.

SIGNED: --------------------------- Patient

WITNESS: --------------------------- (Principal Investigator or Research assistant)

FOMU YA IDHINI

Mimi, ...nimesoma na nimeelewa maelezo niliyopewa kuhusu utafiti huu. Maswali yangu yote yamejibiwa kwa ukamilifu na watafiti. Nimetoa ruhusa kwangu/kwa mwanangu kuhusika katika utafiti huu.

SAHIHI: ------------------------------------ Mhusika

SHAHIDI ------------------------------------ (Mtafiti mkuu/msaidizi):