CLINICAL EVENTS AND CD4 CELL COUNT CHANGES FOLLOWING INITIATION OF ANTIRETROVIRAL THERAPY IN HIV ADULT PATIENTS AT CARE AND TREATMENT CLINIC MBEYA REFERRAL HOSPITAL

By

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A dissertation submitted in partial fulfilment of the requirements for the degree of Master of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied Sciences.

Muhimbili University of Health and Allied Sciences

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I, **Benedicta Nyamizi Masanja,** hereby declare that this dissertation is my own original work and it is a product of my own efforts and that it has not been presented and will not be presented in any other University for a similar or any other degree award.

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DEDICATION

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ABSTRACT

Background: Successful antiretroviral therapy (ART) has changed the outlook of Human Immunodeficient Virus (HIV) patients. However, ART is complicated by adverse drug effects and immune reconstitution inflammatory syndrome (IRIS) events.

Objective: To describe the clinical events and CD4 cell count changes following initiation of ART in HIV adult patients at care and treatment clinic (CTC), Mbeya Referral Hospital (MRH).

Study design and setting: A retrospective follow-up study conducted at the CTC, MRH between April 2007 and August 2007.

Methodology: A standard data collection form was used to collect information from the patients' files and the clinic database.

Results: A total of 1475 HIV patients 61.6% females and 38.4% males were studied. Clinical events characteristic of drug adverse effects were significant after one month of ART and suspected IRIS events were 13.1%, 6.2% and 6.3% at 1, 3 and 6 months following the initiation of ART. No significant difference was seen in the increase in CD4 cell counts by the use of either nevirapine or efavirenz containing regimen. There was a significant association between previous opportunistic infection of TB and the occurence of clinical events of genital ulcers at 3 months following initiation of ART . Other clinical events had no association with previous opportunistic infection. Baseline CD4 cell count of $\leq$ 100 cells/μL and $\geq$101 cells/μL were significantly associated with peripheral neuropathy and abdominal pain 1 month following ART respectively and at 3 months after start of ART peripheral neuropathy was significant among patients with a baseline CD4 cell count of $\leq$ 100 cells/μL.Baseline hemoglobin level of $\geq$12.5 g/dL was significantly associated with hemoptysis after 1 month of ART. At 3 months following initiation of ART patients with a baseline WBC count of $\geq$ 4.5 x 10^3/ μL had significant increase in oral thrush and headache was more at 3 months after

ART among patients with baseline WBC counts of $\leq 4.4 \times 10^3/\mu L$. Chest pain and headache at 6 months after initiation of ART were significant among patients with baseline WBC counts of $\leq 4.4 \times 10^3/\mu L$.

Conclusion and recommendation: Clinical events following the initiation of ART are common and occur due to adverse effects of the drugs but also as suspected IRIS events. Patients starting ART should be closely monitored for adverse drug effects and IRIS especially soon after the start of ART. Prospective clinical studies need to be done to properly diagnose IRIS.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARVs	Antiretrovirals
CMV	Cytomegalovirus
CTC	Care and Treatment clinic
HAART	Highly Active Antiretroviral Therapy
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
IRD	Immune Reconstitution Disease
IRIS	Immune Reconstitution Inflammatory Syndrome
KS	Kaposi's sarcoma
MAC	Mycobaterium Avium Complex
MRH	Mbeya Referral Hospital
MTB	Mycobacterium Tuberculosis
MUHAS	Muhimbili University of Health and Allied Sciences
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NtRTIs	Nucleotide Reverse Transcriptase Inhibitors
NNRTIs	Non Nucleoside Reverse Transcriptase Inhibitors
OI	Opportunistic Infection
PCP	Pneumocystis jiroveci Pneumonia
PIs	Protease Inhibitors
PPE	Pruritc Papular Eruption of HIV
RNA	Ribonucleic acid
UNAIDS	The Joint United Nations Programme on HIV and AIDS
WBC	White Blood Cell
WHO	World Health Organization

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 Background information

HIV infection and Acquired Immunodeficiency Syndrome (AIDS) continue to affect many people worldwide and account for enormous morbidity and mortality. By the end of 2006, The Joint United Nations Programme on HIV and AIDS (UNAIDS)/ World Health Organization estimated that 39.5 million people were living with HIV world wide out of which 37.2 million were adults. There were 4.3 million new infections in that year with 2.8 million of these occurring in sub-Saharan Africa. In 2006, 2.9 million people died of AIDS-related illnesses, 34% of all deaths due to AIDS occurred in sub-Saharan Africa.[1]

In Tanzania about 1.4 million adults and children were living with HIV at the end of 2005. The prevalence of HIV among adult Tanzanians aged 15-49 was reported by The HIV/AIDS Indicator Survey 2003 – 2004 to be 7%. There were regional variations regarding HIV prevalence and the worst affected regions were Mbeya (14%), Iringa (13%) and Dar es Salaam (11%).[1,2]

Infected patients experience various types of clinical events after they start using ART. These can be a result of different adverse effects of the drugs used in the treatment of HIV/AIDS or they can occur as part of reconstituted immunity in the phenomenon of immune reconstitution inflammatory syndrome (IRIS).[3,4] Recommended initial combinations of ART regimens are: (1) 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) with 1 Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI); or (2) 3 NRTIs; or (3) a Protease Inhibitor (PI) with or without low dose ritonavir with 2 NRTIs.[3,5] In Tanzania the recommended drug regimens comprise of 2 NRTIs plus 1 NNRTI or 2 NRTIs and 1 PI. The first line drugs used include Stavudine (d4T), Lamivudine (3TC), Zidovudine (AZT), Nevirapine (NVP) and Efavirenz (EFV). Abacavir (ABC), Didanosine (ddI), Lopinavir/ritonavir and Saquinavir/ritonavir are the second line options for adults and adolescents.[6] Effective ART can result in beneficial immune reconstitution for patients with HIV disease. Since the advent of ART the prognosis

of these patients has dramatically improved as suppression of viral replication and recovery of CD4 T cell counts occur.[4,7] The improved immunity seen is the immunological goal of ART in which there is both qualitative (pathogen specific immune response) as well as quantitative (CD4 cell count in normal range) immune reconstitution. Other goals of ART are virological; with sustained viral suppression, clinical; with improved quality of life and decrease of opportunistic infections, therapeutic; with rational drugs sequencing to facilitate adherence and limit drug toxicity.[8]

In 2004 the government of Tanzania started to provide free ART as part of the national HIV care and treatment program to eligible patients. By December 2006, there were 200 sites providing ART throughout the country with a total of 117,015 patients being enrolled into the program out of which 55,094 were receiving ART.[9] Provision of ART is reported to have expanded dramatically in sub-Saharan Africa whereby more than one million people were receiving antiretroviral treatment by June 2006, a tenfold increase since December 2003.[1]

Information regarding the clinical events following ART as well as the risk factors associated with the occurrence of such events is scarce, especially in Tanzania. As the use of ART is markedly increasing, optimal care of patients receiving ART will need to incorporate monitoring for and treating complications of ART as well as immune reconstitution and hence it is important to explore these issues in order to improve the management of HIV patients on ART.

1.2 Literature review

1.2.1 Clinical events following initiation of ART

It is well established that ART use has significantly reduced HIV related mortality and morbidity[10-12] with patients experiencing decreasing events related to opportunistic infections and death. A study[13] showed overall decline of the incidence of all AIDS defining events after starting ART. Of particular note in that study was that the pattern of decline of AIDS defining

clinical events was most pronounced for events with a viral etiology with a rate of decline of 87.0% per year. The decline in events bearing fungal etiology was the lowest with a rate of 54% per year. However, the mentioned benefits of ART are tempered by various side effects[3, 6, 8] as well as toxicities and adverse events[14] and clinical deterioration due to immune reconstitution.[1415] Therefore the clinical events after initiation of ART can be categorized into two main groups:

1. Antiretroviral drug associated adverse effects.
2. IRIS associated clinical events.

1.2.2 Antiretroviral drug associated adverse effects

Patients using ART commonly suffer from adverse effects of specific drugs in their ART regimens hence the treatment of HIV infection needs to balance between the benefits of durable HIV suppression and the risks of drug toxicity. It is also known that the incidence of adverse reactions is high in the initial ARV therapy and tends to decrease in later stages, when long term reactions may occur.[16] About 25 % of patients stop therapy within the first year on HAART because of side effects.[17] A study[18] in New Orleans attributed ART adverse events as a cause for switch or discontinuation of ART in 24% of patients. Several adverse events after the initiation of ART were also seen among patients in a study[19] done in Brazil whereby at least one adverse event was reported after initiation of ART. The majority of the patients in that study received triple regimens including two NRTI plus one NNRTI or one PI. The most common adverse events were nausea and vomiting in 14.5% and 13.1% respectively. Others were diarrhea in 8.9%, headache in 2.8%, fever in 1.9%, nightmares in 1.4%, dizziness in 4.2%, anemia 6.5%, fatigue 2.8%, and heartburn/stomach pain in 3.7%. A higher incidence of adverse reactions to ARV was also seen among patients who had at least one AIDS related diagnosis before the first ARV prescription and, among those who switched the ARV regimen or the non-adherent ones. Most of the adverse reactions occurred before the fourth month of therapy compatible with the incidence of acute, common and nonspecific events after ART initiation.

The study[16] showed the use of PI sparing regimens to be associated with greater risk of vomiting, sleep and mood disorders, and increased concentrations of amylase, but reduced risk of diarrhea, and increased concentrations of bilirubin and urate. In that study, 3TC was associated with lipodystrophy and mood disorders, d4T with lipodystrophy and headache, and rise in serum concentrations of creatine phosphokinase, lactate, urate, cholesterol, and triglyceride. Anemia was associated with AZT use and neutropenia with concomitant use of AZT and 3TC while ddI was associated with increase in urate and lactate concentrations and ABC with vomiting and increase in creatine phosphokinase concentrations.

Drug combinations in ART

Drugs available for use in the treatment of HIV infection fall into four different classes namely:

1. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs and NtRTIs)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)
4. Fusion inhibitors

The drugs are available as individual agents or combined as fixed dose agents. Nucleoside and nucleotide analogs include drugs such as Lamivudine (3TC), Zidovudine (AZT), Stavudine (d4T), Abacavir (ABC), Didanosine (ddI), Emtricitabine (FTC), Zalcitabine (ddC) and Tenofovir disoproxil fumarate (TDF). Combined agents in this class are Combivir (AZT + 3TC), Epzicom (3TC + ABC), Trizivir (AZT + 3TC + ABC) and Truvada (FTC + TDF). NRTIs are important components of almost all combination regimens. They are converted to the active metabolite only after endocytosis, whereby they are phosphorylated to triphosphate derivatives. They are easy to take and their overall tolerability is fairly good. Elimination is mainly by renal excretion and they do not interact with drugs that are metabolized by hepatic enzymes. However, frequent complaints during the first weeks of therapy are fatigue, headache and gastrointestinal problems, which range from mild abdominal discomfort to abdominal pain, nausea, vomiting and diarrhea.[3,8] The long-term side effects are reported to

be myelotoxicity, lactate acidosis, polyneuropathy and pancreatitis. Lipodystrophy and especially lipoatrophy is attributed to nucleoside analogs.[20]

Mitochondrial toxicity develops in some patients following the use of NRTIs and NtRTIs. Patients with underlying organ dysfunction such as chronic liver disease, prior pancreatitis, concomitant opportunistic disease, and administration of other drugs with similar toxicity profiles are among the factors associated with the development of mitochondrial toxicity. As NRTIs and NtRTIs are phosphorylated intracellularly to active triphosphate forms, then incorporated into new DNA strands synthesized by HIV reverse transcriptase, the lack of a 3' hydroxyl in NRTIs and NtRTIs results in HIV DNA chain termination. Therefore the major toxicities of NRTIs and NtRTIs therapy, in the medium to long term, may be secondary to inhibition of mitochondrial DNA polymerase leading in impaired synthesis of mitochondrial enzymes that generate ATP by oxidative phosphorylation. Such adverse effects include myopathy with AZT and clinically patients will have fatigue, myalgia, proximal weakness and wasting. Neuropathy occurs with drugs such as d4T and ddI whereby the presentation is of distal pain, numbness, parasthesia, reduced reflexes and power. With the exception of 3TC and ABC, the rest of the NRTIs and NtRTIs may cause hepatic steatosis and lactic acidosis. Patients present with nausea, dyspnoea, ascites, and hepatomegaly, raised liver enzymes, raised lactic acidaemia and reduced bicarbonate levels. Peripheral lipoatrophy is possibly seen with all NRTIs; however it is very commonly seen in patients using d4T. Pancreatitis is much more associated with the use of ddI. Mitochondrial toxicities usually have gradual onset although they may occur within days of ART initiation.[21]

Taking Stavudine as a prototype in the NRTIs class, it is a thymidine analog which is often initially tolerated well with less gastrointestinal side effects and limited myelotoxicity. The dosage is 40mg or 30mg twice daily for body weights above and less than 60kgs respectively. Oral bioavailability is 86% and has no food effects. The adverse effects associated with Stavudine include peripheral neuropathy which occurs at a frequency of 5% to 15%. The onset usually noted at 2 to 6 months of therapy and resolves after stopping the medication.

Lactic acidosis and steatosis are reported in 1 to 14/1000 patient years of NRTI exposure. Clinical presentation is with nausea, fatigue, abdominal pain, vomiting, weight loss and dyspnoea. Another adverse effect of d4T is HIV associated neuromuscular weakness syndrome. This presents as an ascending motor weakness in a small number of patients receiving this drug. Other recognized adverse effects of d4T are headache, esophageal ulcers and gastrointestinal intolerance with diarrhea.[3,8]

Drugs in the NNRTI class include Nevirapine (NVP), Efavirenz (EFV) and Delevirdine (DLV). In contrast to NRTIs, they do not require activation within cells. When used in combination with NRTIs they are very effective. Dosing is simple and due to good overall tolerability NVP and EFV are important components of many ART regimens. Metabolism is via the cytochrome p450 system hence dose adjustments are necessary when co-administered with drugs such as PIs occurs. NVP is a cytochrome p450 inducer whereas DLV is a cytochrome p450 inhibitor and EFV is a mixed inhibitor and inducer of the cytochrome p450 system. The common side effects of NNRTIs include rash and hepatotoxicity. Other side effects are headache and central nervous system affection with EFV whereby reported complaints include dizziness, confusion, abnormal dreams, insomnia and hallucinations. These resolve within 2 – 3 weeks.

Drug hypersensitivity is common with ART and in HIV patients is about 100 times more common than in the general population. It can manifest with an erythematous, pruritic, maculopapular and confluent rash with or without fever. However, rash seen at more than 8 weeks after start of ART, is almost always due to another cause. Stevens Johnson syndrome or toxic epidermal necrolysis develops in less than 0·5% of patients. All NNRTIs, Abacavir and Amprenavir are associated with hypersensitivity unlike other drugs in their respective classes.[21]

Considering Nevirapine as the representative drug of the NNRTIs class, it binds directly and non-competitively to reverse transcriptase and blocks the RNA dependent and DNA

dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The adult dose is 200mg twice daily however; a lead in dosing with 200mg daily in the first two weeks of beginning therapy is required. Oral bioavailability of NVP is over 90% and there are no food effects. Elimination is 80% excreted in urine. The adverse effects of NVP include rash which occurs in 15% to 30% of those initiating NVP and leads to NVP discontinuation in 7%.[22] With isolated rash or isolated elevated transaminases therapy can be continued. However treatment should be discontinued in the case of rashes with even slightly elevated transaminases such as more than two fold of the normal values.[3] Rare cases of Stevens Johnson syndrome due to NVP may occur. The drug is hepatotoxic and elevation in liver enzymes occurs in about 20%, this may occasionally be severe. Hepatic necrosis can occur especially in women with a CD4 cell count at baseline of more than 250 cells per micro liter.[8]

Protease inhibitors include the following drugs, Indinavir (IDV), Saquinavir (SQV), Nelfinavir (NFV), Ritonavir (RTV), Lopinavir/ritonavir (LPV), Atazanavir (ATV), Fosamprenavir (FVP), Amprenavir (APV) and Tipranavir (TPV). These drugs prevent cleavage of gag - pol protein precursors in acutely and chronically infected cells hence no proteolytic splicing or maturation occurs and hence there is release of virus particles which are unable to infect new cells. PIs have revolutionalized treatment of HIV infection especially for the treatment experienced patients. Apart from gastrointestinal side effects and high pill burden, all PIs used in long term therapy face problems associated with lipodystrophy and dyslipidemia.[23] Pathogenesis of lipodystrophy is not known. It might be due to inhibition of adipocyte and lipid regulatory proteins with partial homology to the catalytic site of HIV protease enzyme to which the PIs bind.[21] Mitochondrial toxicity of NRTI has also been linked to some features of lipodystrophy syndrome. Lipodystrophy manifests with peripheral fat loss in the face, limbs, and buttocks and central fat accumulation within the abdomen, breasts, and over the dorsocervical spine. Metabolic features associated with lipodystrophy and PI therapy include hypertriglyceridaemia, hypercholesterolemia, insulin resistance and type 2 diabetes mellitus. These metabolic abnormalities are more profound in those receiving protease

inhibitors. Drug interactions are very common and the use of ritonavir boosted PIs is recommended. Ritonavir is a very potent inhibitor of the isoenzyme 3A4, a subunit of the cytochrome p450 hepatic enzyme system thus in small doses it leads to increased plasma levels of all PIs except Nelfinavir whose plasma concentration does not rise significantly upon boosting with ritonavir.[3]

An example of a PI that is also used as a second line option for the treatment of HIV in Tanzania is Lopinavir/ritonavir (Kaletra). The dose is 133mg LPV and 33mg RTV capsules for adults. It is recommended to be taken with food; however the bioavailability has not been determined. The drug requires refrigeration for storage and is stable in room temperature for 2 months. It is both an inhibitor and inducer of the cytochrome p450 system. The drug's adverse effects include dyslipidemia which is more marked than with most other PIs, lipodystrophy and gastrointestinal problems such as nausea, vomiting and diarrhea.[8]

Enfuvirtide is the first available fusion inhibitor for the treatment of HIV. It binds to the heptad repeat (HR1) site in the glycoprotein (gp41) subunit of the viral envelope glycoprotein and prevents conformational change required for viral fusion and entry into cells. The drug has potent antiviral activity with no resistance in patients not previously treated with it. It is administered subcutaneously at an adult dose of 90mg (1 mL) twice daily and requires concurrent use of drugs from other classes of ARVs to avoid monotherapy. The major side effect is injection site reactions such as pain, erytherma, pruritus and induration.[8]

1.2.3 IRIS associated clinical events

Defining IRIS is difficult, it is generally a clinical diagnosis made by linking the typical clinical findings unique to the specific OI related IRIS to a temporally related; ART induced increase in absolute CD4 cell count. It is estimated that 10% - 25% of patients who start ART experience IRIS. In these patients there is symptomatic deterioration of pre-existing sub clinical infections that become symptomatic after the recovery of the immune response and the consequent inflammatory response to certain pathogens. The spectrum of the syndrome is

very diverse and, associated infections are those due to *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, *Mycobaterium avium complex,* cytomegalovirus, *Pneumocystis jirovecci*, hepatitis B and C as well as herpes zoster and Kaposi's sarcoma.[15,24-26]
How immune reconstitution disease develops is not yet well understood, in particular whether similar mechanisms are involved in response to different pathogens. The specific immune response against microbial antigens appearing shortly following the initiation of ART may either represent adequate inflammatory response that was previously masked by severe immunodeficiency or an overshooting inflammatory reaction.[7]

Despite the variety of infections associated with IRIS, some patterns can help distinguish IRIS and an ordinary OI. There are major and minor criteria used for the diagnosis of IRIS. The major criteria are A and B and, a diagnosis of IRIS would require both major criteria or criterion A and two minor criteria.

Major criteria

A. Atypical presentation of opportunistic infections or tumours in patients responding ART

- Localised disease e.g. lymph nodes, liver, spleen.
- Exaggerated inflammatory reaction e.g. severe fever, with exclusion of other causes, painful lesions.
- Atypical inflammatory response in affected tissues e.g. granulomas, suppuration, necrosis, perivascular lymphocytic inflammatory cell infiltrate.
- Progression of organ dysfunction or enlargement of pre-existing lesions after definite, clinical improvement with pathogen specific therapy prior to commencement of ART and exclusion of treatment toxicity and new diagnoses e.g. development of enlargement or cerebral space occupying lesions after treatment for cerebral Cryptococcus or Toxoplasmosis.
- Progressive pneumonitis or the development of organising pneumonia after treatment for pulmonary TB or PCP.
- New onset or worsening of uveitis/vitritis after resolution of CMV retinitis.

- Fever and cytopenia after treatment for disseminated Mycobacterium avium complex (MAC) disease.
- Enlargement of Kaposi's sarcoma lesions and subsequent resolution or partial regression without commencement of radiotherapy, systemic chemotherapy or intralesional therapy.

B. Decrease in plasma HIV RNA level by >1 log10 copies/mL.

Minor criteria

- Increase blood CD4+ cell count after HAART.
- Increase in immune response specific to the relevant pathogen e.g. delayed type hypersensitivity to mycobacterial antigens.
- Spontaneous resolution of disease without specific antimicrobial therapy or tumour chemotherapy with continuation of anti-retroviral therapy.

Risk factors for IRIS

The risk factors for IRIS include co infection with MTB, MAC or C. neoformans. ART naïve patients who commence HAART closer to the diagnosis of an OI also have a risk of developing this syndrome and, therefore should be closely monitored[26]. Severe immunodeficiency at the start of ART with a CD4 count of less than fifty is another clue of a patient's risk especially for the more serious events. However, some patients with higher CD4 cell counts at the start of treatment may still develop certain IRIS disorders especially skin problems.[24,27] Other risk factors include male sex, more rapid initial fall in HIV RNA on ART[21] and higher HIV RNA at ART initiation.[28]

Onset of IRIS

The interval between the start of ART and the onset of IRIS is highly variable ranging from less than one week to several months; however majority of the events occur within the first eight weeks after ART initiation.[25,29] Some IRIS illnesses may be biphasic with an initial

reaction occurring the first few weeks or months after treatment begins, and a related event due to the same infection or at the same site occurring months or years later.

Immune reconstitution manifestations by pathogen

***Mycobacterium tuberculosis* IRIS**

The most common pathogen associated with IRIS is MTB. About 36% of HIV/MTB co-infected patients developed paradoxical responses on anti TB treatment and ART.[30,31] Patients have severe inflammatory reactions including fever, worsening of pulmonary conditions, shortness of breath, and enlargement of lymph nodes or cerebral masses, spinal lesions and tuberculous meningitis. Others are weight loss, abdominal TB IRIS with abdominal pain and obstructive jaundice. Presentation of TB IRIS is within the first two months of HAART, usually in the first 2-3 weeks.[30,32] Therefore clinicians need to be highly suspicious of TB IRIS soon after ART initiation. Paradoxical central nervous system (CNS) TB also occurs in HIV patients, however, TB associated CNS IRIS clinically occurs much later at about 5 - 10 months following the initiation of ART. In the study[30] on paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS, HIV patients treated with anti TB therapy and HAART had a higher incidence of paradoxical reactions with new fever; worsening or emergence of lymphadenopathy, pleural effusion, pulmonary infiltrates or worsening of other tuberculous lesions than HIV patients not treated with HAART. In their case reports on five consecutive HIV infected patients with IRIS due to mycobacterial infection[33] showed that clinical and radiological deterioration occurred between 10 days and 7 months following the initiation of HAART, with unmasking of previously undiagnosed mycobacterial infection or to worsening of mycobacterial disease. The patients had HAART-induced rises in CD4 cell counts and reductions in HIV viral load. Radiographic abnormalities due to IRIS included marked severe mediastinal lymphadenopathy leading to tracheal compression, new pulmonary infiltrates and pleural effusion.

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Mycobacterium avium complex IRIS

Mycobacterium avium intracellular complex (MAI or MAC) has not been widely perceived as a serious opportunistic infection in most resource-limited settings, because it is such a late-stage disease event that patients usually die of other causes before developing MAC symptoms. However, atypical mycobacteria are frequent causative pathogens in IRIS and their frequency increased with the introduction of protease inhibitors[34] as well as the general introduction of ART. Apparently, MAC infections are often present without leading to symptoms, but while symptomatic MAC before ART was generally a systemic disease often associated with a non-specific form or wasting MAC IRIS is a localized disease, focusing one part of the body. It may cause swollen or inflamed lymph nodes or organ. It might also cause ulcers in the gastrointestinal tract or skin abscesses.[35]

Cryptococcus associated IRIS

The incidence of cryptococcal associated IRIS is not known and, many represent reactivation of past treated cases.[36] Therefore they are suggestive of inflammatory reaction to residual antigens or immunological reaction to partially treated disease. IRIS-related cryptococcosis was observed more frequently in severely immunocompromised patients with disseminated infection and HAART initiation soon after the diagnosis.[36-38] Another study[39] whereby patients with *C. neoformans* related IRIS meningitis were compared to typical AIDS related *C. neoformans* meningitis, the patients with *C. neoformans* related IRIS meningitis had higher baseline HIV RNA levels, higher WBC counts and glucose levels, higher cerebrospinal fluid Cryptococcal antigen titers and opening pressure. Clinically they did not differ in presentation. Meningitis, palsy, hearing loss, abscess, lymphadenitis, and mediastinitis may be the presenting features of cryptococcal induced IRIS.

Hepatitis B and C viruses

In a study[24] HBV IRIS was demonstrated in four patients. Presentation was either asymptomatic or symptomatic with fever, nausea and vomiting with abnormal liver function tests and increasing HBV titers and increasing HBsAg titers over 3 – 6 months. Liver biopsy

in one patient showed chronic hepatitis with moderate activity. Regarding hepatitis associated with HCV infection, another study[28] demonstrated symptomatic hepatitis in three patients. These had an increase in serum alanine transaminase 5 times higher than the upper reference range limit. Two patients seroconverted from HCV antibody negative to positive after HAART and, on examination of stored plasma it was demonstrated that HCV RNA had been present for about 12 months before commencing therapy. Their liver biopsies had evidence of chronic hepatitis without esinophilia or granulomata.

Varicella zoster virus

Dermatomal varicella zoster comprises 9 – 40% of IRIS cases[24,27,28] and occurred from about five weeks after the initiation of ART. Risk factor for developing dermatomal varicella zoster was noted to be significant increases in CD8 T cells. Other complications like myelitis, encephalitis, acute retinal necrosis, cranial and peripheral nerve palsies can also occur.

Cytomegalovirus

Before ART, CMV retinitis had high incidence and was among the most significant morbidities in AIDS. With the introduction of ART new types of eye problems, usually CMV related such as uveitis or inflammation within the back part of the eye (vitritis), among people who had previously been treated for CMV retinitis within a year of starting ART occurred. The HAART induced inflammatory response unmasked a sub clinical infection.[40] Distinct from minimal intraocular inflammation of the classic CMV retinitis, manifestations seen with HAART had significant posterior segment ocular inflammation due to the presence of residual CMV proteins or antigens.[41]

Kaposi's sarcoma

Kaposi's sarcoma (KS) is the most common tumor in people infected with HIV. It remains a significant cause of morbidity and mortality in such patients. The causative pathogen is Human Herpes virus 8 or Kaposi's sarcoma associated herpes virus (KSHV).[42] IRIS is a well recognized complication of infection with another herpes virus, cytomegalovirus. HAART

has been shown to decrease the incidence of KS,[42] and lead to resolution of individual lesions.[43-45] It also decreases KSHV viral load. These are possible features why IRIS can occur with KSHV infection. A study[46] showed IRIS associated KS in 6.6%. KS IRIS was demonstrable in patients with higher CD4 counts, therapy with both non nucleosides and protease inhibitors together and as well with KS associated edema. The clinical presentation of KS IRIS is with flares of the lesions and rises in CD4 count and fall in HIV viral load during the flares.[47]The mean time of onset of the KS IRIS is 5 weeks after ART and may be observed as early as 3 weeks with most cases diagnosed within 2 months after HAART.

CD4 cell counts and first line ART regimens

In ART naïve patients commencing therapy, the CD4 cell count increase is about 100 – 150 cells per micro liter in the first year of treatment. During the initial months of ART there is an accelerated increase in CD4 cell count and a steady increase is observed up to about four years after initiation of ART.[48,49] The study[50] that involved severely immunosuppressed individuals with CD4 cell counts of <50 cells/mm^3 showed that CD4 cell count increases were related to virological control, with continuing increases seen in patients who were immunosuppressed. The rate of increase in CD4 cell counts in that study was about 5.9 cells/mm^3 every 8 weeks. Increases in CD4 counts from very low levels to at least 200 cells/mm^3 were associated with a much reduced rate of disease progression.[51] Considering the different ART regimens used, a study[52] found that regimens containing AZT and 3TC or any TDF based backbone were associated with poorer increases in CD4 cell count compared to a nucleoside backbone of d4T and 3TC, as was an ABC containing triple nucleoside regimen compared to a boosted PI regimen. In comparing first line ART regimens that contained either NVP or EFV, another study[53] showed the two had similar efficacy. Another study[54] compared the immunological response to highly active antiretroviral therapy in treatment naive patients with a baseline CD4 count of <200 cells/mm^3. The drug regimens used had a nucleoside reverse transcriptase backbone and either a PI or NNRTI analogue. It concluded that PI and NNRTI based regimens were not significantly different in achieving increased CD4 counts in individuals who start therapy with a low CD4 cell count. Furthermore NVP and EFV

containing ART regimens as initial therapy in patients with advanced HIV infection were found to be effective and comparable, in terms of both immunological and as well virological responses.[55]

2.0 STATEMENT OF THE PROBLEM

The use of antiretroviral therapy is associated with the development of different adverse effects which are reported to be very common especially during the first weeks of initiating therapy.[3,8] These can be moderate but in some instances life threatening.[14] About 25% of patients stop ART within the first year on ART due to side effects.[17]

It is also estimated that 10% - 25% of patients who start ART experience IRIS. In these patients there is symptomatic deterioration of pre-existing sub-clinical infections that become symptomatic after the recovery of the immune response and the consequent inflammatory response to certain pathogens. The spectrum of the syndrome is very diverse and, associated infections are those due to *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, *Mycobaterium avium complex,* cytomegalovirus, *Pneumocystis jirovecci*, hepatitis B and C as well as herpes zoster and Kaposi's sarcoma.[15,24,25,28]

It is anticipated that IRIS will become more frequent as antiretroviral therapy becomes available in less developed countries, where the underlying prevalence of *M. tuberculosis, C. neoformans,* and hepatitis B is high and where patients initiating antiretroviral therapy are more likely to have advanced immunodeficiency.

As there is limited local data on clinical events following the initiation of ART and, the increasing coverage of antiretroviral therapy in the country it is necessary to ascertain the occurrence of such events and to understand why they develop in some patients. This will improve HIV care and treatment through developing preventative and treatment strategies to reduce the complications of ART.

3.0 RATIONALE

Management of HIV infection with the use of highly active antiretroviral therapy is complicated by occurrence of common adverse effects attributed to specific agents incorporated in the different combinations of ART regimens.[3,8] Furthermore IRIS after commencing ART may cause misinterpretations both on the part of the patients and doctors, if patients are reluctant to start ART in fear of adverse effects they might assume that IRIS is proof for the justification of their doubts. On the other hand, doctors could mistakenly assume poor patient compliance, treatment failure or resistance and this might especially be true with IRIS when ART and OI treatment are concomitantly initiated.

There is scarcity of data on the clinical events characteristic of ART adverse effects and inflammatory response after the start of ART in Tanzania. The majority of our HIV patients are ART naïve hence at risk of developing symptoms and signs documented elsewhere to be part of the immunological and virological responses to HIV treatment[15,26] and adverse effects of ART.[21] Moreover our patients begin ART with advanced immunosuppression; which is another reported risk for clinical deterioration after starting ART.[26]

In an attempt to increase the wealth of knowledge on this topic, as there are no large prospective clinical trials, the aim of this study was to describe the clinical events after initiation of ART and associate them with the proposed occurrences of signs and symptoms of reconstituted immunity and the ART adverse effects.

4.0 STUDY OBJECTIVES

4.1 Broad objective

To describe the clinical events and CD4 cell count changes following initiation of antiretroviral therapy in HIV patients at care and treatment clinic, Mbeya Referral hospital.

4.2 Specific objectives

1. To describe the occurrence of clinical events by social demographic characteristics of the study population.
2. To determine the association between documented baseline CD4 cell counts and other laboratory findings with subsequent clinical events following initiation of ART.
3. To determine the relationship between previous illnesses/opportunistic infections and the occurrence of clinical events following initiation of ART.
4. To determine the association between antiretroviral drug regimen and CD4 cell count changes.

5.0 METHODOLOGY

5.1 Description of study area

The study was conducted at Mbeya Referral Hospital which is a tertiary level hospital situated within Mbeya city in Mbeya region. The region is located in the southern highlands of Tanzania and is bordered by Zambia and Malawi to the immediate south, Rukwa region to the west, and Tabora and Singida regions to the north while Iringa region lies to the east. As a referral hospital it is serving 4 regions in the southern highlands namely Mbeya, Iringa, Rukwa and Ruvuma. The care and treatment services for HIV and AIDS patients are well established within the hospital and ART for HIV patients started in 2004. About 2300 patients were receiving ART between October 2004 and October 2006.

5.2 Study design

Retrospective follow-up study.

5.3 Study population

The study comprised of HIV patients who started antiretroviral therapy between October 2004 and October 2006 at the CTC of Mbeya referral hospital.

5.4 Inclusion criteria

1. ART naïve
2. 18 years or above
3. Started ART between Oct 2004 and Oct 2006 at the care and treatment clinic, MRH

5.5 Sample size

The sample size was determined using the formula: -

$$n = \frac{N z^2 p (1- p)}{d^2 (N- 1) + z^2 p (1 - p)}$$

Where;

N = total population of patients who started antiretroviral therapy between October 2004 and October 2006 at MRH which was 2300

z = z value corresponding to the confidence level of 95% which is 1.96

d = absolute precision set at 2%

p = expected proportion of patients with clinical events characteristic of IRIS which is 10%

Therefore;

$$n = \frac{2300 \times 1.96^2 \times 0.1\ (1-0.1)}{0.02^2\ (2300-1) + 1.96^2 \times 0.1\ (1-0.1)}$$

$$n = 628$$

Therefore the minimum calculated sample was 628.

5.6 Sampling procedure

Two thousand and three hundred patients who started ART between October 2004 and October 2006 were considered. A total of 1703 patients met the inclusion criteria, data was collected consecutively in 1475 patients hence the calculated sample was about doubled and reached 1475. Thus with a sample size of 1475 patients there was more than sufficient statistical power to detect the probability of a type one error on assessing statistical significance at the 95% probability level.

5.7 Research instruments and data collection procedures

A standard prepared data collection form (Appendix 1) was used to obtain from the patients files and the CTC database, the sociodemographic information, baseline laboratory values namely CD4 cell counts, CBC and ALT, previous opportunistic infections, current illnesses and ART regimens at the time of ART initiation and events during follow up in the general examination, gastrointestinal tract (GIT), respiratory system (RS) ,cardiovascular system (CVS), central nervous system (CNS) and the skin. The files were retrieved from the CTC records office by the investigator using patients' files identification numbers and names as they appeared in the generated list of patients that met the inclusion criteria.

Data was collected from April to August 2007 when the investigator visited the study site twice, first in April 2007 for the feasibility study and training of research assistants who assisted on the collection of the laboratory investigations. The second visit to the field was from July to August 2007 in which the investigator singularly collected the data by reviewing the patients' records and filling in the required information in the data collection forms.

5.8 Data management and analysis

Upon completion of a day's work the investigator checked the collected data on the forms for completeness. Subsequently the data was entered, cleaned and analyzed using EPI INFO 6 Version 6.04 and SPSS Version 11.0. Clinical events were expressed in percentages for the entire study population. To reduce the skewness in laboratory values of blood tests including CD4 cell counts, CBC and ALT which are not normally distributed, median and the interquartile ranges were used. Mean (SD) was used as a measure of central tendency for age and body weights. Chi square was used to determine the association of occurrence of clinical events among patients at different times of follow up from initiation of ART. The Mann Whitney nonparametric test of two independent samples was used to determine the association between changes in CD4 cell count from baseline by NVP or EFV based regimen. A p value of 0.05 or less was taken to indicate a significant statistical association.

5.9 Ethical clearance

Ethical and research clearance was obtained from the Higher Degree Research and Publication Committee of the Muhimbili University of Health and Allied Sciences. Permission to conduct the study was sought from Mbeya Referral Hospital authorities.

5.10 Definition of terms

A clinical event in this study was defined as:

1. Any symptom and/or sign reported to occur and/or worsen after the start of ART.
2. Recurrent disease if the patient had previous history of same disease.

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3. Any new diagnosis made after start of ART.

Antiretroviral therapy/ highly active antiretroviral therapy was defined as use of any of the following regimens as per Tanzania National Guidelines for the clinical management of HIV and AIDS:

- Stavudine + Lamivudine + Nevirapine
- Zidovudine + Lamivudine + Nevirapine
- Stavudine + Lamivudine + Efavirenz
- Zidovudine + Lamivudine + Efavirenz
- Abacavir + Didanosine +Lopinavir/ritonavir or Saquinavir/ritonavir

Suspected IRIS: if a patient presented at 1month after ART with either fever, lymph node enlargement, cough, TB, pneumonia, pleural effusion, herpes zoster or meningitis or if a patient presented at 3 and 6months after ART with either fever, lymph node enlargement, cough, TB, pneumonia, pleural effusion, herpes zoster or meningitis and a rise in CD4 cell count from the baseline CD4 count.

Hemoglobin level of 12.5g/dL was defined as the normal level of hemoglobin for adults according to WHO criteria.

For this study WBC from 4.5 x $10^3/\mu L$ was considered normal. The MRH laboratory uses Sysmex/Coulter machine for complete blood count and reports normal white blood cell count from 4.5 x $10^3/\mu L$.

6.0 RESULTS

6.1 Characteristics of the study population at baseline

A total of 1475 patients among the 2300 patients that started ART at the CTC of Mbeya Referral Hospital between October 2004 and October 2006 were studied out of whom 61.6% were females. The mean age of the study population was 38.2 (SD 9.5) years, with the range of 18 – 78 years. The majority of the subjects (71.9%) had a primary level of education while secondary and post secondary education attainment levels were observed in 17.4%. One hundred and fifty seven subjects (10.6%) had no formal education. Over one half of the studied subjects (58.1%) were married/ cohabiting and 20.1% were widows. Two hundred and seventeen (14.7%) and one hundred and four (7.1%) were single and divorced respectively. Regarding past opportunistic infections, 22.2% had a previous history of tuberculosis while 11.2% had a past history of herpes zoster. The mean body weight at initiation of antiretroviral therapy was 53.3kg (SD 10.2). The median baseline CD4 cell count was 103cells/μL (interquartile range 39-169 cells/ μL). Other baseline laboratory tests were only available in 1455 subjects for the hemoglobin level, 1029 subjects for the total WBC, 1024 subjects for the platelet count and 1005 subjects for the ALT level. The median Hb, WBC, PLT and ALT with their respective interquartile ranges were 10.5g/dL (9.1-11.7g/dL), 4.5 $x10^3/\mu L$ (3.4-5.8 $x10^3/\mu L$), 255 $x10^3/\mu L$ (186-334 $x10^3/\mu L$) and 20.7 U/L (13.4-32.8 U/L) respectively. One thousand thirteen hundred and sixty seven subjects (92.7%) were started on a regimen consisting of d4T, 3TC and NVP. The rest 3%, 0.3% and 4% were initiated regimens containing d4T, 3TC and EFV, AZT, 3TC and NVP and AZT, 3TC and EFV respectively. Table 1 presents the characteristics of patients at ART initiation.

Table 1: Baseline characteristics of HIV adult patients at CTC-MRH who started antiretroviral therapy between October 2004 and October 2006 (N=1475)

Characteristic	Number	Percentage
Sex		
Female	908	61.6
Male	567	38.4
Marital Status		
Married/Cohabiting	857	58.1
Single	217	14.7
Divorced	104	7.1
Widows	297	20.1
Education		
No formal Education	157	10.6
Primary Education	1061	71.9
Secondary/Post Secondary Education	257	17.4
Previous OIs		
Tuberculosis	327	22.2
Herpes Zoster	165	11.2
ART regimen		
d4T 3TC NVP	1367	92.7
d4T 3TC EFV	44	3.0
AZT 3TC NVP	5	0.3
AZT 3TC EFV	59	4.0
Blood tests	Median (interquartile range)	
CD4 count cells/μL	103	(39-169)
*WBC × 10^3/μL N=1029	4.5	(3.4-5.8)
*Hb g/dL N=1455	10.5	(9.1-11.7)
*PLT× 10^3/μL N=1024	255	(186-334)
*ALT U/L N=1005	20.7	(13.4-32.8)
Age years mean(SD)	38.2 (±9.5)	
Body weight kg mean(SD)	53.3 (±10.2)	

* There were some missing data for some of the subjects.

6.2 Clinical events

Table 2 summarizes the clinical events noted at various time intervals following the initiation of ART. Fever occurred in 3.7% of the patients that were seen after one month of therapy compared to 2.6% who complained of fever at baseline. This difference was not statistically significant ($p=0.08$). However, with advancing time on ART the occurrence of fever decreased significantly ($p<0.001$). The mean body weight increased significantly ($p<0.001$) with increased duration on ART.

Overall, after one year of ART, the number of patients reporting gastrointestinal tract (GIT) events studied namely, diarrhea, vomiting, abdominal pain, oral thrush and odynophagia decreased significantly ($p<0.001$). However, it was interesting to note that, the decrease was preceded by a significant increase in frequencies to some of these GIT events at one month of ART (Table 2). Diarrhea events at one month rose ($p=0.03$) as were vomiting and abdominal pain which increased significantly at this duration ($p<0.001$) and ($p=0.01$) respectively. Odynophagia was noted in 3.3% at one month compared to 0.9% at the start of ART, this difference was statistically significant ($p<0.001$).

With regard to the respiratory system, cough was reported more frequently by patients (9.7%) at one month of ART as compared to 8.3% at the initiation of ART. However, the difference was not statistically significant. On the contrary, on further follow-up at three to twelve months of ART, the proportion of patients reporting cough significantly declined ($p<0.001$). In addition, chest pain and pneumonia decreased significantly ($p<0.001$ and $p=0.01$ respectively) after the initiation of ART during the patients' follow-up. Although it was not reported by any patient at the initiation of ART, hemoptysis occurred in a small proportion of patients; at first 2 (0.2%), third 1 (0.1%) and sixth months 1 (0.1%) follow-up. Tuberculosis was noted to decrease significantly ($p<0.001$) from baseline to one month after the start of ART. Clinicians made the diagnosis of Tuberculosis less often at first month of ART compared to at the time of ART initiation.

The clinical events affecting the skin included rash (unspecified dermatological conditions), PPE, KS, genital ulcers and herpes zoster. These with the exception of genital ulcers and herpes zoster decreased significantly with advancing duration of time after the start of ART ($p<0.001$) for rash (unspecified dermatological conditions), ($p<0.001$) for PPE and ($p=0.03$) for KS. There was no significant difference in the occurrences of genital ulcers and herpes zoster in the twelve months of ART (Table 2).

In the cardiovascular system, shortness of breath decreased significantly ($p<0.001$) following the initiation of ART. However, the difference observed in events of palpitations and edema was not statistically significant ($p=0.2$).

Headache significantly increased after one month of ART ($p=0.003$) however the subsequent difference observed at three, six and twelve months was not statistically significant ($p=0.3$). Peripheral neuropathy was noted to increase significantly following the initiation of ART with advancing durations of follow up ($p<0.001$).

Table 2: Occurrence of clinical events among HIV adult patients at CTC-MRH following initiation of ART between October 2004 and October 2006 (N=1475)

Event	Duration										P value
	Baseline N=1475		1month N= 1232		P value	3months N= 1071		6months N=936		12months N=708		
	N	%	N	%		N	%	N	%	N	%	
General												
Fever	39	2.6	45	3.7	0.08	15	1.4	20	2.1	10	1.4	***
Nodes	0	0.0	7	0.6		2	0.2	3	0.3	0	0.0	
Body weight kg mean(SD)	53.3 (±10.2)		55.2(±10.3)			56.9(±10.2)		59.6(±10.0)		61.3(±10.3)		***
GIT												
Diarrhea	64	4.3	76	6.2	0.03	48	4.5	10	1.1	10	1.4	***
Vomiting	14	0.9	72	5.8	***	25	2.3	0	0.0	0	0.0	***
Abd pain	74	5.0	91	7.4	0.01	46	4.3	9	1.0	8	1.1	***
Oral thrush	29	2.6	11	0.9	***	7	0.7	1	0.1	0	0.0	***
Odynophagia	14	0.9	41	3.3	***	9	0.8	1	0.1	0	0.0	***
RS												
Cough	122	8.3	120	9.7	0.2	55	5.1	40	5.6	26	3.7	***
Hemoptysis	0	0.0	2	0.2		1	0.1	1	0.1	0	0.0	
Chest pain	62	4.2	25	2.0	0.001	24	2.2	8	1.1	13	1.4	***
Pneumonia	19	1.3	9	0.7	0.2	7	0.7	3	0.3	1	0.1	0.01
TB	51	3.5	7	0.6	***	0	0.0	0	0.0	0	0.0	
PCP(clinical)	3	0.2	3	0.2	0.8	0	0.0	0	0.0	0	0.0	
Skin												
Rash(unspecified)	75	5.1	43	3.5	0.04	35	3.3	21	2.2	10	1.4	***
PPE	57	3.9	57	4.6	0.3	45	4.2	21	2.2	12	1.7	***
KS	57	3.9	44	3.6	0.6	36	3.4	24	2.6	11	1.6	0.03
Genital ulcer	6	0.4	7	0.6	0.5	7	0.7	2	0.2	2	0.3	0.5
H. Zoster	1	0.1	0	0.0		2	0.2	1	0.1	1	0.1	
CVS												
SOB	4	0.3	13	1.1	0.01	3	0.3	1	0.1	1	0.1	***
Palpitations	1	0.1	6	0.5	0.07	2	0.2	2	0.2	1	0.1	0.2
Oedema	8	0.5	7	0.6	0.7	2	0.2	1	0.1	1	0.1	0.2
CNS												
Headache	58	3.9	79	6.4	0.003	46	4.3	45	4.8	31	4.4	0.3
Peripheral neuropathy	32	2.2	62	5.0	***	114	10.6	135	14.4	85	12.0	***
Meningitis	2	0.1	2	0.1		1	0.1	0	0.0	0	0.0	
Suspected IRIS			161	13.1		66	6.2	59	6.3			***

***P < 0.001

6.3 Suspected Immune Reconstitution Inflammatory Syndrome

One hundred and sixty one patients (13.1%) out of those seen after one month following ART had suspected IRIS as shown on (Table 2). This occurred in 6.2% and 6.3% of those seen at three and six months respectively. There was a significant decrease in suspected IRIS from the first month through the sixth month following the initiation of ART ($p<0.001$).

6.4 CD4 cell count changes

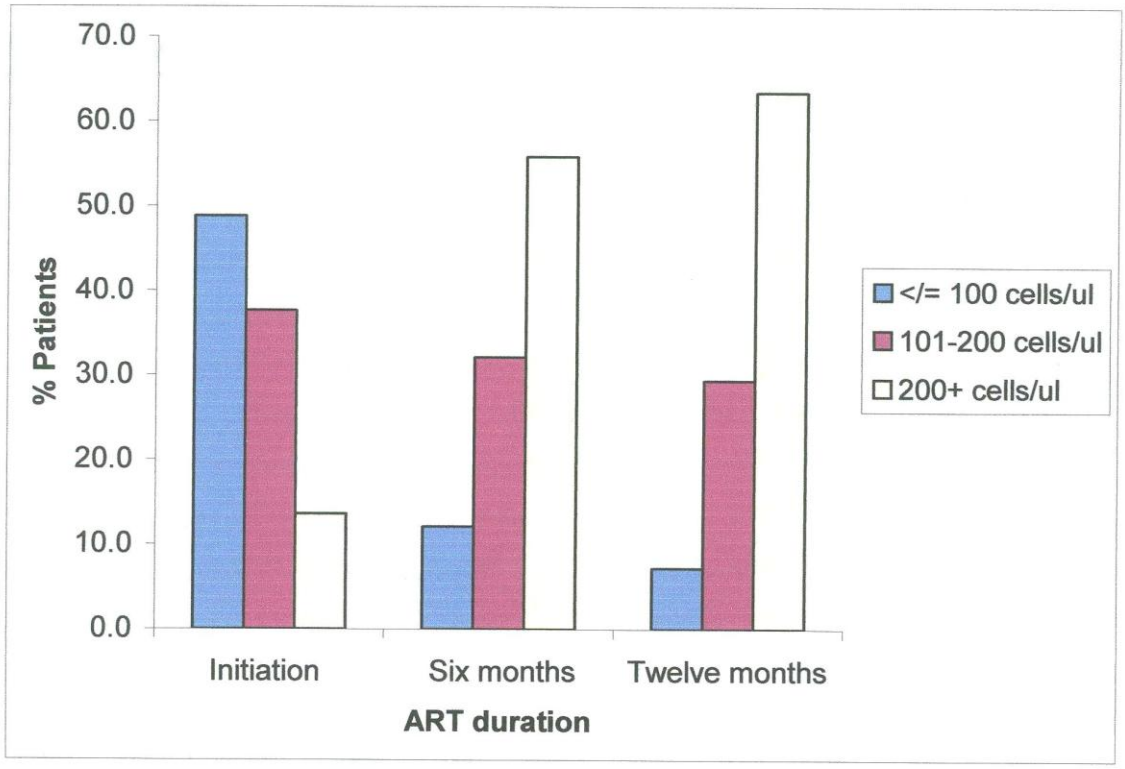


Figure 1: Absolute CD4 cell count changes with ART duration among HIV adult patients who started ART between October 2004 to October 2006 at CTC-MRH (N =1475)

Figure 1 above depicts that majority of the patients improved immunologically (as indicated by CD4 cell count increase) with increase in ART duration. Approximately half of the

patients had absolute CD4+ T Lymphocyte count of less or equal to 100 cells/uL at ART initiation compared to only 7.2% of the patients in the same category at 12 months of ART. On the other hand, the proportion of patients with absolute CD4 cell counts of more than 200 cells/uL steadily increased with increase in ART duration.

6.5 Change in CD4 cell count from baseline by Nevirapine or Efavirenz containing regimen

At baseline one thousand three hundred and seventy two (93%) patients were started on a NVP containing regimen while 7% were initiated an EFV based regimen. Their median CD4 cell counts were 122.5 cells/μL (interquartile range 27.3-274.0 cells/μL) and 69.0 cells/μL (interquartile range21.3-158.3cells/μL) respectively. The difference in the median CD4 cell counts at baseline were statistically significant (p=0.005) for the two regimens. The change in CD4 cell count at three months after ART was noted to be much higher in the EFV group from a median of 69.0 cells/μL at baseline to that of 283.0 cells/μL. During that time CD4 cell counts were available in ninety four subjects. In the NVP containing group at three months after ART patients had a rise of CD4 cell count from a median of 122.5 cells/μL to 227.0 cells/μL. Nevertheless the noted changes were not statistically significant (p=0.66). There was leveling off and a decrease in the change in CD4 cell count in both groups at the sixth month however the counts increased at twelve months after ART medians being 248.0 cells/μL and 241.3 cells/μL in the NVP and EFV containing regimens respectively. However no statistical significance was noted in the changes of CD4 cell counts between the two regimen during the follow up intervals of three, six and twelve months after the initiation of ART (Table 3).

Table 3: Change in CD4 cell count from baseline by regimen; Nevirapine or Efavirenz containing

Duration	ART regimen		P value
	NVP containing	EFV containing	
Baseline N=1475 median cells/μL (interquartile range)	1372 122.5 (27.3-274.0)	103 69.0 (21.3-158.3)	0.005
3 months N=94 median cells/μL (interquartile range)	83 227.0 (151.0-369.0)	11 283.0 (125.4-452.3)	0.66
6 months N=591 median cells/μL (interquartile range)	553 220.0 (152.5-334.5)	38 202.0 (129.6-383.4)	0.43
12months N=524 median cells/μL (interquartile range)	495 248.0 (170.0-365.0)	29 241.3 (162.8-350.8)	0.9

6.6 Association between documented baseline CD4 cell counts and other laboratory tests with subsequent clinical events following initiation of ART

Among the patients seen after 1 month from the start of ART, 561 (46.2%) had a baseline CD4 cell count of ≤ 100 cells/μL while 663 (53.8%) had a baseline CD4 cell count of ≥101 cells/μL. In these patients abdominal pain was more in patients who had higher CD4 cell count ≥101 cells/μL at the start of ART than in those who had a baseline CD4 cell count of ≤ 100 cells/μL at (9.8%) and (5.3%) respectively (Table 4). This difference was statistically significant (p=0.002) (Table 4). Peripheral neuropathy at 1 month after initiation of ART was observed more in patients who had a baseline CD4 count of ≤ 100 cells/μL (7.0%) than those with a baseline CD4 count of ≥101 cells/μL (3.3%) and the difference was statistically significant, p = 0.003 (Table 4). There were no significant differences in other clinical events at 1 month in terms of occurrence among patients who had a baseline CD4 cell count ≤ 100 cells/μL or ≥101 cells/μL (Table 4). In patients seen at 3 months from the initiation of ART, 493 (46.0%) had baseline CD4 cell count of ≤ 100 cells/μL while 578 (54.0%) had baseline CD4 cell count of ≥101 cells/μL. Peripheral neuropathy was observed more in patients who had a baseline CD4 cell count of ≤ 100 cells/μL (13.8%) than in those who initiated ART with a CD4 cell count of ≥101 cells/μL (8.0%) and, the difference was statistically significant (p = 0.002) (Table 4). Other clinical events at 3 months after ART had no significant difference in

occurrence among patients with CD4 cell counts of ≤ 100 cells/μL or ≥101 cells/μL at the initiation of ART (Table 4). At 6 months after the start of ART there were no significant differences in the occurrence of clinical events based on the baseline CD4 cell count category of ≤ 100 cells/μL or ≥101 cells/μL (Table 4).

Table 4: Occurrence of clinical events by baseline CD4 counts among HIV adult patients at CTC-MRH following initiation of ART between October 2004 and October 2006

Characteristic	Duration								
	1 month			3 months			6 months		
Baseline CD4 cell cont cells/μL	≤100 N=569 N %	≥101 N=663 N %	P	≤100 N=493 N %	≥101 N=578 N %	p	≤100 N=415 N %	≥101 N=521 N %	p
Fever	23 (4.0)	22 (3.3)	0.50	5 (1.0)	10(1.7)	0.32	7 (1.7)	13 (2.5)	0.39
Diarrhea	42 (7.4)	34 (5.1)	0.10	22 (4.5)	26(4.5)	0.98	4 (1.0)	6 (1.2)	0.78
Abd pain	31 (5.3)	56 (9.8)	0.002	23 (4.7)	23(4.0)	0.58	2 (0.5)	7 (1.3)	0.18
Oral thrush	6 (1.1)	5 (0.8)	0.58	3 (0.6)	4 (0.7)	0.87	0 (0.0)	1 (0.2)	0.37
Cough	49 (8.6)	53 (8.0)	0.69	15 (3.0)	25(4.3)	0.27	13 (3.1)	22 (4.2)	0.38
Chest pain	10 (1.8)	15 (2.3)	0.53	11 (2.2)	13(2.2)	0.98	8 (1.9)	5 (1.0)	0.21
Pneumonia	3 (0.5)	6 (0.9)	0.44	2 (0.4)	5 (0.9)	0.35	2 (0.5)	1 (0.2)	0.44
Hemoptysis	1 (0.2)	1 (0.2)	0.91	0 (0.0)	1 (0.2)	0.36	0 (0.0)	1 (0.2)	0.37
Headache	42 (7.2)	37 (5.6)	0.20	23 (4.7)	23(4.0)	0.58	24 (5.8)	21 (4.0)	0.21
P. neuropathy	40 (7.0)	22 (3.3)	0.003	68 (13.8)	46(8.0)	0.002	61 (14.7)	74(14.2)	0.82

Table 5: Occurrence of clinical events by baseline hemoglobin level among HIV adult patients at CTC-MRH following initiation of ART between October 2004 and October 2006

Characteristic	Duration								
	1 month			3 months			6 months		
Baseline Hb g/dL	≤12.4 N=1041 N %	≥12.5 N=174 N %	P	≤12.4 N=893 N %	≥12.5 N=161 N %	p	≤12.4 N=777 N %	≥12.5 N=143 N %	p
Fever	40 (3.8)	5 (2.9)	0.53	13 (1.5)	2 (1.2)	0.83	17 (2.2)	3 (2.1)	0.94
Diarrhea	65 (6.2)	10 (5.7)	0.80	43 (4.8)	4 (2.5)	0.19	8 (1.0)	2 (1.4)	0.69
Abd pain	77 (7.4)	9 (5.2)	0.29	40 (4.5)	3 (1.9)	0.12	8 (1.0)	0 (0.0)	0.22
Oral thrush	8 (0.8)	2 (1.1)	0.61	7 (0.8)	0 (0.0)	0.26	1 (0.1)	0 (0.0)	0.67
Cough	86 (8.3)	15 (8.6)	0.87	34 (3.8)	6 (3.7)	0.96	29 (3.7)	6 (4.2)	0.79
Chest pain	23 (2.2)	2 (1.1)	0.36	18 (2.0)	6 (3.7)	0.18	12 (1.5)	1 (0.7)	0.43
Pneumonia	7 (0.7)	2 (1.1)	0.49	7 (0.8)	0 (0.0)	0.26	2 (0.3)	1 (0.7)	0.39
Hemoptysis	0 (0.0)	2 (1.1)	0.001	1 (0.1)	0 (0.0)	0.67	1 (0.1)	0 (0.0)	0.67
Headache	72 (6.9)	6 (3.4)	0.08	39 (4.4)	7 (4.3)	0.99	37 (4.8)	8 (5.6)	0.67
P. neuropathy	57 (5.5)	5 (2.9)	0.15	100(11.2)	12(7.5)	0.16	119(15.3)	15(10.5)	0.13

Table 5 above shows the occurrence of clinical events by baseline Hb level among patients following initiation of ART. Among patients seen at 1, 3 and 6 months after the start of ART baseline Hb values were available for 1215, 1054 and 920 patients at those intervals respectively. Most patients, 1041 (85.7%), 893 (84.7%) and 777 (84.5%) at 1, 3 and 6 months from the initiation of ART had baseline Hb levels ≤12.4 g/dL respectively. Hemoptysis was observed more (1.1%) in patients with baseline Hb levels of ≥12.5 g/dL and, the difference between them and those with a baseline Hb level of ≤12.4 g/dL was statistically significant (p = 0.001) at 1 month following the initiation of ART . The table shows that the other clinical events namely fever, diarrhea, abdominal pain, oral thrush, cough, chest pain, pneumonia, hemoptysis, headache and peripheral neuropathy had no statistical significant differences in occurrence following the initiation of ART at the specified periods of time based on the patients' baseline Hb levels.

Table 6: Occurrence of clinical events by baseline white blood cell count among HIV adult patients at CTC-MRH following initiation of ART between October 2004 and October 2006

Characteristic	Duration								
	1 month			3 months			6 months		
Baseline WBC x $10^3/\mu L$	≤4.4 N=422 N %	≥4.5 N=430 N %	p	≤4.4 N=370 N %	≥4.5 N=371 N %	p	≤4.4 N=314 N %	≥4.5 N=329 N %	p
Fever	10 (2.4)	20 (4.7)	0.07	7 (1.9)	4 (1.1)	0.36	6 (1.9)	7 (2.1)	0.85
Diarrhea	37 (8.8)	32 (7.4)	0.48	20 (5.4)	23 (6.2)	0.64	4 (1.3)	6 (1.8)	0.57
Abd pain	41 (9.7)	35 (8.1)	0.42	19 (5.1)	20 (5.4)	0.87	5 (1.6)	3 (0.9)	0.44
Oral thrush	3 (0.7)	7 (1.6)	0.21	0 (0.0)	7 (1.9)	0.01	0 (0.0)	1 (0.3)	0.33
Cough	47 (11.1)	54 (12.6)	0.52	16 (4.3)	24 (6.5)	0.19	17 (5.4)	16 (4.9)	0.75
Chest pain	10 (2.4)	15 (3.5)	0.33	13 (3.5)	11 (3.0)	0.67	10 (3.2)	2 (0.6)	0.02
Pneumonia	3 (0.7)	6 (1.4)	0.33	2 (0.5)	5 (1.3)	0.26	2 (0.6)	1 (0.3)	0.54
Hemoptysis	0 (0.0)	2 (0.5)	0.16	0 (0.0)	1 (0.3)	0.32	0 (0.0)	1 (0.3)	0.33
Headache	35 (8.3)	24 (5.6)	0.12	24 (6.5)	12 (3.2)	0.04	22 (7.0)	11 (3.4)	0.04
P. neuropathy	23 (5.5)	22 (5.1)	0.83	48 (13.0)	39(10.5)	0.29	52 (16.6)	41 (12.5)	0.14

Table 6 above summarizes the occurrence of clinical events by baseline WBC count level following the initiation of ART. In patients seen at 1 month after initiation of ART, there were no significant differences in the occurrence of the clinical events based on their baseline WBC

count whether ≤4.4 x 10^3/ µL or ≥4.5 x 10^3/ µL. At 3 months following the initiation of ART, no patient with a baseline WBC count of ≤4.4 x 10^3/ µL had oral thrush. However, at this duration 1.9% of those with baseline WBC count of ≥4.5 x 10^3/ µL presented with oral thrush. This difference was statistically significant (p = 0.01). The occurrence of headache at 3 months after initiation of ART was more among patients who had a baseline WBC count of ≤4.4 x 10^3/ µL (6.5%) than in those with a baseline WBC count of ≥4.5 x 10^3/ µL (3.2%), the difference was statistically significant (p = 0.04). Chest pain and headache at 6 months after ART were observed more among patients with baseline WBC count of ≤4.4 x 10^3/ µL (3.2%) and (7.0%) respectively. The differences in occurrence of these events among these patients and those with baseline WBC counts of ≥4.5 x 10^3/ µL were statistically significant with p values of 0.02 and 0.04 respectively (Table 6). The other clinical events seen at 6 months after ART had no statistical significant difference between patients with a baseline WBC count of ≤4.4 x 10^3/ µL or ≥4.5 x 10^3/ µL.

6.7 Relation between previous opportunistic infection and occurrence of clinical events following initiation of ART

Table 7 below shows the relation between past opportunistic infection of TB and the occurrence of clinical events following initiation of ART. Among the patients seen after 1 month of ART, 283 (23.0%) had a past history of TB while 949 (77.0%) did not have that past history. Forty patients (4.2%) out of the 949 who had no previous history of TB were observed with rash at 1 month following the start of ART. During that time rash was observed in 1.1% of the patients with a past TB history. This difference was statistically significant (p = 0.01). Although other clinical events as shown in Table 7 at 1 month duration after the start of ART occurred at a relatively higher rate among patients with previous TB than those without that history, the differences were statistically not significant. At 3 and 6 months following the initiation of ART, 246 patients (23%) and 217 patients (23.2%) had past TB respectively. Out of the clinical events seen at 3 and 6 months, only genital ulcer occurred more in patients with past TB and the differences were statistically significant with p values of 0.002 and 0.01 at 3 and 6 months respectively following the start of ART (Table 7). The table shows that all other

remaining clinical events at 3 and 6 months after initiation of ART had no significant difference of occurrence based on a positive or negative past TB history.

Table 7: Relation between past opportunistic infection of TB and occurrence of clinical events among HIV adult patients at CTC-MRH following initiation of ART between October 2004 and October 2006

Characteristic	Duration								
	1 month			3months			6 months		
Past TB	YES N=283 N %	NO N=949 N %	p	YES N=246 N %	NO N=825 N %	p	YES N=217 N %	NO N=719 N %	p
Fever	12 (4.2)	33 (3.5)	0.55	3 (1.2)	12 (1.5)	0.78	4 (1.8)	16 (2.2)	0.73
Vomiting	20 (7.1)	52 (5.5)	0.32	5 (2.0)	20 (2.4)	0.72	0 (0.0)	0 (0.0)	x
Diarrhea	18 (6.4)	58 (6.1)	0.88	14 (5.7)	34 (4.1)	0.29	3 (1.4)	7 (1.0)	0.61
Abd pain	26 (9.2)	65 (6.8)	0.19	10 (4.1)	36 (4.4)	0.84	3 (1.4)	6 (0.8)	0.47
Oral thrush	3 (1.1)	8 (0.8)	0.73	1 (0.4)	6 (0.7)	0.58	1 (0.5)	0 (0.0)	0.07
Cough	27 (9.5)	75 (7.9)	0.38	10 (4.1)	30 (3.6)	0.76	8 (3.7)	27 (3.8)	0.96
Hemoptysis	0 (0.0)	2 (0.2)	0.44	0 (0.0)	1 (0.1)	0.59	0 (0.0)	1 (0.1)	0.58
Chest pain	5 (1.8)	20 (2.1)	0.72	8 (3.3)	16 (1.9)	0.22	4 (1.8)	9 (1.3)	0.51
Pneumonia	1 (0.4)	8 (0.8)	0.39	2 (0.8)	5 (0.6)	0.72	1 (0.5)	2 (0.3)	0.68
Rash	3 (1.1)	40 (4.2)	0.01	6 (2.4)	29 (3.5)	0.41	5 (2.3)	16 (2.2)	0.95
H. Zoster	0 (0.0)	0 (0.0)	x	0 (0.0)	2 (0.2)	0.44	0 (0.0)	1 (0.1)	0.58
PPE	11 (3.9)	46 (4.8)	0.50	10 (3.9)	35 (4.2)	0.9	6 (2.8)	15 (2.1)	0.55
Genital ulcer	1 (0.4)	6 (0.6)	0.58	5 (2.0)	2 (0.2)	0.002	2 (0.9)	0 (0.0)	0.01
Headache	14(4.9)	65 (6.8)	0.25	13 (5.3)	33 (4.0)	0.38	15(6.9)	30 (4.2)	0.10
Meningitis	1 (0.4)	1 (0.1)	0.36	0 (0.0)	1 (0.1)	0.59	0 (0.0)	0 (0.0)	x
P. neuropathy	11 (3.9)	51(5.4)	0.32	28 (11.4)	86 (10.4)	0.67	30(13.9)	105(14.6)	0.79

[x] No statistics computed as no patient presented with the event

7.0 DISCUSSION

The aim of this study was to describe the clinical events and CD4 cell count changes following the initiation of antiretroviral therapy in HIV patients who were attending the care and treatment clinic at Mbeya Referral Hospital in Mbeya region.

This study showed two types of clinical events. The first category of events was noted early on after commencing treatment. At one month the gastrointestinal events had increased in frequency compared to baseline. During that time, vomiting, abdominal pain and diarrhea increased significantly. These events were due to adverse effects resulting from the consumption of antiretroviral drugs which have been shown to be associated with a number of adverse effects.[3,8,19] All patients at the initiation of therapy received first line drugs according to the Tanzania national guidelines for the clinical management of HIV and AIDS with 2 NRTIs plus 1 NNRTI. This is a standard recommended best practice when ART is considered especially in naïve patients[3,6,8] as the ones involved in this study. The majority of the patients, 93%, started treatment with a Nevirapine containing regimen with 92.7% of them using d4T, 3TC and NVP and 0.3% using AZT, 3TC and NVP. The remaining 7% were on an EFV based regimen with 3% using d4T, 3TC and EFV and 4% using AZT, 3TC and EFV. As a class, the NRTIs have been implicated in the causation of a number of a number of gastrointestinal adverse effects including nausea, vomiting abdominal pain and diarrhea.[3,8,21]These are reported to be common during the first weeks of beginning ART and in this study at one month (four weeks) there was a significant increase of the mentioned events. Hence it is most likely they occurred as a result of ART adverse effects. Other events that were observed to rise significantly at one month included headache and odynophagia. Since Stavudine has been shown to cause headache and esophageal ulcers,[3] it can explain this observation. However, as the frequency of oral thrush decreased from a baseline of 2.6% to 0.9% at one month, linking candidiasis with odynophagia at that time was difficult and the responsible agent may remain to be Stavudine. Peripheral neuropathy was also noted to increase significantly from one month after ART up to twelve months. Again as Stavudine

was being used by over two third of the study patients and, it is among the well established causative agents for peripheral neuropathy in the long term[21] reported to occur in 5% -15% of those initiating Stavudine containing regimen. Peripheral neuropathy as a long term adverse effect was seen after 12 months of ART in these patients.

The second type of clinical events observed in this study were those seen to be mostly of a suspected immune reconstitution origin. There was an increase of fever from 2.6% at the start of ART to 3.7% one month later. Fever is a common feature of IRIS. Fever is also known to be a common symptom of inflammation and appears in acute inflammatory processes of infectious and non infectious origin. In cases of inflammation of infectious origin, fever is non pathogen specific. The increase in the incidence of fever a month after initiation of ART in this study was highly probable that it was due to IRIS.

Immune reconstitution inflammatory syndrome is pathogen specific[26,28,30] and clinically as patients continue therapy, several clinical features can occur to mimic specific diseases such as TB, meningitis, and others described in IRIS. The increase in the frequency of fever at one month coupled with the presence of lymph node enlargement, cough, shortness of breath, pleural effusion, pneumonia, herpes zoster and cryptococcal meningitis were observed in 13.1% of patients seen at one month after ART. Appearing that soon, these events were suspected to be due to reconstituted immunity. Since CD4 cell counts were not routinely performed at one month after ART and HIV viral loads were also not routinely done to support the diagnosis of IRIS, the term suspected IRIS was used. However, at three and six months following the initiation of ART, CD4 cell count measures were available in some patients. Those who had an increase in the CD4 cell count from the baseline value at three and six months after ART and presented with the other mentioned features above were categorized to also have suspected IRIS. This was observed in 6.2% and 6.3% after 3 and 6 months of ART respectively.

This study with the frequency of suspected IRIS of 13.6% seems to be similar to those reported by other researchers of about 10%-25% in patients starting ART.[26] A recent prospective study in South Africa[56] reported the incidence of IRIS to be 10.4%. Depending on pathogens involved, rates as high as 30% have been reported.[30] The retrospective design of this study could have underestimated the incidence of IRIS in this group of patients, it was not designed to look for specific IRIS related conditions.

Patients involved in this study had risk factors known to be associated with the development of IRIS; they had advanced immunodeficiency with median CD4 cell count of 103 cells/μL at the beginning of ART, were ART naïve and had previous history of opportunistic illnesses such as tuberculosis 22.2% and herpes zoster 11.2%. Other studies[26,28] also showed that lower CD4 cell count at ART initiation, being ART naïve, shorter interval between opportunistic infection therapy initiation and ART initiation to be the risk factors for development of IRIS.

In this study, clinical events significantly decreased as the duration of ART increased. This is supported by the study that showed declining morbidity with the use of highly active antiretroviral therapy[10]. It is also very well established that the use of ART dramatically changes the outlook for HIV infected patients showing clinical as well as immunological and virological improvement with proper use of ART.

CD4 cell counts improved from their baseline levels, after 6 and 12 months of ART for patients who had available CD4 cell counts, the counts for those who had ≤ 100 cells/μL decreased from 48.8% at baseline to 12.1% after 6 months and to a further 7.2% after 12 months. The proportion of those who had CD4 cell count between 101-200 cells/μL decreased from 37.6% at the initiation of ART to 32.1% after 6 months and to 29.4% at 12 months. Fewer patients (13.6%) had CD4 cell count of 200+ cells/μL at the start of ART, their percentage increased at six and twelve months respectively to 55.8% and 63.4%. A number of studies have shown that the use of ART is associated with immunological improvement including a rise in CD4 cell counts, a feature observed in this study. The use of ART results

in reduction of HIV viral load and reduced destruction of CD4 cells. Hence, the balance between CD4 cell destruction by the HIV and CD4 cell production by the body allows the increase in the number of CD4 cell counts.

Patients received either NVP or EFV containing regimens, the NVP containing regimen comprised 93% at the start of therapy and EFV containing regimen in 7%. At the start of therapy the CD4 cell counts differed significantly being much lower (69.0 cells/μL) in the EFV group compared to 122.5 cells/μL in the NVP group. This observation may presumably be explained by the differential proportion of TB co-infections within the two groups. Indeed, in our country, HIV patients on concomitant treatment for TB are usually kept on EFV based HAART regimen, this therefore, may explain the lower CD4 cell counts in this group of patients attributable to co-morbidity of HIV and TB which have been shown to be commonly associated with lower CD4 cell counts.[57] Moreover, in accord with previous studies,[53,55] absolute T-lymphocyte CD4 count change with ART duration in the patients on NVP based regimens did not differ from that observed in patients on EFV based regimen suggesting similar effectiveness in immunological responses of the two drugs. This is also seen in this study.

Regarding occurrence of clinical events based on some baseline laboratory values, most had no significant difference in terms of events occurring at different levels of baseline laboratory values. However, baseline CD4 cell count of $\leq$ 100 cells/μL were significantly associated with peripheral neuropathy and abdominal pain 1 month following ART respectively and at 3 months after start of ART peripheral neuropathy was significant among patients with a baseline CD4 cell count of $\leq$ 100 cells/μL. HIV associated neuropathy may be the cause of the early presentation of neuropathy but Stavudine associate peripheral neuropathy could account for the increase in the peripheral neuropathy.

Baseline hemoglobin level of $\geq$12.5 g/dL was significantly associated with hemoptysis after 1 month of ART. Although this was significant the number of patients presenting with it was

very small hence generalization should be made very cautiously. At 3 months following initiation of ART patients with a baseline WBC count of $\geq 4.5 \times 10^3/\ \mu L$ had significant increase in oral thrush and headache was more at 3 months after ART among patients with baseline WBC counts of $\leq 4.4 \times 10^3/\ \mu L$. The study could not explain these observations. Chest pain and headache at 6 months after initiation of ART were significant among patients with baseline WBC counts of $\leq 4.4 \times 10^3/\ \mu L$. Previous opportunistic infections especially with TB had no association with the subsequent occurrence of clinical events following the initiation of ART except for presentation of genital ulcers at 3 months after ART. Similarly the study could not explain this observation. Moreover the finding should be applied cautiously as the number with genital ulcer and a past history of TB at 3 months after starting ART was very small.

8.0 STUDY LIMITATIONS

This study depended on collecting data on information already existing in the records after patients had been started on ARVs at the care and treatment. This could have a bias on attending clinicians' interpretation and handling of the patients' complaints. The CTC patients follow up forms were uniform and this could overcome the bias and as well the large sample that was studied may have generated reliable information. As viral loads were not routinely measured at the time of this study, proper definition of IRIS was not possible as this crucial parameter could not be incorporated.

Liver function tests on patients follow up visits were not done routinely. No tests were done for Hepatitis B or C. As majority of patients were on a Nevirapine containing regimen, determination of subsequent Nevirapine or viral hepatitis associated hepatotoxicity could not be possible.

9.0 CONCLUSIONS

1. Anti Retroviral Therapy (ART) was associated with improved patients' immune status.
2. Following initiation of ART patients presented with clinical events due to ART adverse effects commonly of the gastrointestinal system and suspected IRIS.
3. More clinical events presented during the first month following the initiation of ART.
4. Clinical events decreased significantly with increase in duration of ART.
5. Suspected IRIS occurred more frequently (13.1%) at 1 month following the start of ART, but was less oberved after 3 and 6 months follwing initiation of ART at frequencies of 6.2% and 6.3% respectively .

10.0 RECOMMENDATIONS

Clinicians attending HIV patients should be more careful early on after putting patients on ARVs to monitor and treat the ART associated clinical events as well as IRIS so as to improve the quality of life of the patients.

I recommend prospective clinical studies to be undertaken so as to time the clinical events after the initiation of ART as well as properly define IRIS.

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