A review of clinical and immunological outcomes as predictors of viral loads among children on HAART for at least 24 weeks at the University Teaching Hospital, Lusaka, Zambia

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A dissertation submitted to the University of Zambia in partial fulfillment of the degree of Masters in Public Health

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Certificate of Approval

This dissertation of Dr. Rokaya Ginwalla-Lakhi is approved as fulfilling the requirement for the award of the degree of Masters of Public Health in internal Medicine by the University of Zambia.

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I, **Dr C.Kankasa**, having submitted and read this dissertation, am satisfied that this is the original work of the author under whose name it is being presented. I confirm that the work has been completed satisfactorily and is hereby ready for presentation to the examiners.

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ABSTRACT

Title: A review of clinical and immunological outcomes as predictors of viral load response among children on HAART for at least 24 weeks at the University Teaching Hospital, Lusaka, Zambia

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Objectives: To determine the prevalence of clinical, immunological and virological failure in children on HAART for more than 24 weeks and see how well the clinical, immunological parameters can predict virological response in children HAART at the University Teaching Hospital in Lusaka.

Methods: Retrospective chart review of routinely collected patient data from a cohort of HIV positive children and adolescents between 0 to 19 years, who had received ART for more than 24 weeks and had at least one documented viral load test result. For the period September 2005 to August 2011 every second patient file with viral load result was chosen systematically for analysis and data was collected using a form designed to capture every six monthly clinical visit with the corresponding laboratory results.

Results: A total of 517 files were reviewed. Clinical parameters (WHO staging, BMI Z-score and hemoglobin were not good predictors of viral load response. Immunological parameter, (CD4 count or age related CD4%), was a good predictor of virological response (p value 0.01 and 95% CI - 0.49 to -0.29). However this prediction was only positive for 68% of patients while the majority with a positive prediction fell in the category where VL <1000, for those with VL $\geq$ 1000, CD4 criteria was a poor predictor of failure.

Conclusions: Routine viral load testing in the HIV treatment program in Zambia will help prevent multiple drug resistance mutations with early appropriate second-line treatment. It will also prevent premature drug changes, thus preserving future option.

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- All patients enrolled in the paediatric ART program

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List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-Retroviral Therapy
BMI Z-score	Body Mass Index Z-Score
CD4	Helper T-cells
DBS	Dried Blood Spot
FDC	Fixed Dose combination
HAART	Highly Active Anti-Retroviral Therapy
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
MoH	Ministry of Health
P-ART	Paediatric Anti-Retroviral Therapy
PCOE	Paediatric Centre of Excellence
PITC	Provider Initiated Testing and Counselling
UNAIDS	Joint United Nations Program on HIV/AIDS
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Emergency Fund
UNZA	University of Zambia
UTH	University Teaching Hospital
VL	Viral Load
WHO	World Health Organization

APPENDIX IV

TITLE: A review of immunological and virological outcomes among children on HAART for at least 24 weeks at the University Teaching Hospital, Lusaka, Zambia

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BACKGOUND: There is increasing evidence that the current clinical and immunological monitoring tools are not sufficient to identify early enough patients who are failing on treatment. Development of resistance to the limited treatment options for children and premature switching are the dangers. The objective of this study was to review patient records to see how well CD4 profiles and viral load estimations relate in children.

METHODS:A retrospective chart reviews of all children aged between 0-19 years that started treatment between January 2004 and Dec 2010 was carried out at the University Teaching Hospital. Systematic sampling was done of every second child who received HAART for more than 24 weeks and with at least one viral load reading after 24 weeks of treatment. Six-monthly immunological and virological data were collected until last follow-up review or five years on treatment The 2010 Zambian Pediatric Guidelines were used to gauge age-related immunological and virological failure (viral load > 1,000).

RESULTS: A total of 517 patient records were reviewed. Mean age at ART initiation was 7 years ((SD 4.7yrs). Mean time after ART initiation when first viral load test was done was 2.7 years (SD 1.5yrs). Of all the viral loads done, 64% (328) had a routine indication for patients on treatment nearing the 3 year mark. In 40% ofchildren the first viral load test result was above 1,000 after 24 weeks or more of treatment. 23% of the patients (121) were consistently failing immunologically and virologically; 48% (246) were consistently not failing; 20% (104) had a high CD4, but failing virologically and 6% (30) had a low CD4 but were virologically suppressed.

CONCLUSIONS: Immunological monitoring in children on ART does not accurately identify those that are failing. A push for routine, affordable virological testing is needed to identify treatment failures early to prevent development of ART resistance and avoid premature switches to second line.

CHAPTER 1

1.0 Introduction:

The 2009 UNAIDS AIDS Epidemic update report showed that Sub-Saharan Africa remains the region most heavily affected by HIV accounting for 67 percent of HIV infections worldwide, 68 percent of new HIV infections among adults and 91 percent of new HIV infections among children. The region also accounted for 72 percent of the world's AIDS-related deaths.

The report showed that the number of children less than 15 years living with HIV/AIDS was 2.1 million, of which 1.8 million reside in sub-Saharan Africa. Children accounted for 6 percent of all HIV infections, 17 percent of new infections and 14 percent of all AIDS deaths in the same year (Joint UNICEF WHO, UNAIDS stocktaking report, 2009). In sub-Saharan Africa the number of people receiving ART increased more than tenfold between 2003 and 2007. However, only 34 percent of children in need are receiving ART; accounting for 6 percent of the nearly 3 million people on treatment (Joint UNICEF, WHO, UNAIDS, UNFPA 2009).

Regular plasma HIV viral load testing is part of the standard of care for the follow-up of HIV-infected children in the developed world. However, in most resource-limited settings, including Zambia, the decision to initiate and monitor ART in children and adolescents relies on clinical and/or immunological assessment. As the scale up of pediatric ART programs continues and children stay on treatment for a longer period of time, more information is needed to define the optimal treatment monitoring modality in both adults and children. Increasingly, older children are becoming the face of the pediatric HIV

epidemic and many perinatally infected children have now reached adolescence (Merzel, 2008).

1.1 Description of the National Pediatric ART program and UTH PCOE

The Pediatric ART program in Zambia was launched in 2004 when it was realized that a large number of children infected through mother-to-child transmission, were dying early as a result of lack of treatment. The year 2007 was a major milestone for the Pediatric ART (P-ART) program: two Pediatric ART program officers were appointed at the Ministry of Health (MoH) to manage Pediatric care and treatment at national level; the Zambia National P-ART guidelines and the Zambian Pediatric Training Manual were produced to train health care workers; the Ministry of Health (MoH) issued guidance on routine provider initiated testing and counseling (PITC) for all children in health care settings; the MoH began to train health care workers country-wide; improved availability of pediatric formulations at district level hospitals including fixed dose combinations (FDC's). Finally, in 2007, three Polymerase Chain Reaction (PCR) referral laboratories became functional alongside a training program for collection of dried blood spot (DBS). However viral load testing in Zambia is limited to very select patients failing clinically and immunologically on first or second line therapy and patients under study conditions. Currently only two centers, UTH and Kalingalinga laboratories, have the capacity to perform this test.

In 2009, Zambia reported an estimated 76,000 children living with HIV and 34,000 in immediate need of antiretroviral therapy. By the end of 2010, 25,000 children were

accessing ART contributing to 8 percent of all Zambians receiving treatment (MoH,pediatric 2011 report). The Department of Paediatrics and Child Health at the University Teaching Hospital (UTH) was among the first sites in Zambia to provide treatment to children.Implementation of routine provider initiated counseling and testing at the UTH, contributes to over 95 percent of children testing and large numbers referred to the care and treatment program. At initiation of the program, clinical outcomes and CD4 counts were used as the mainstay of monitoring patient progress. To date close to 4,000 children have received treatment in the UTH program. Most of these children were perinatally infected and with early intervention, many have survived into adolescence and adulthood. Routine clinical and immunological monitoring is carried out at least once every six months.

Since September 2007, the laboratory capacity has improved and viral load testing is performed on a case by case basis as well as for patients who have been on HAART for 3 years or more. To date over 1,000 samples have been tested, yet no analysis has been done on the levels of viral suppression, or the relationshipbetween the viral load and routine parameters used (CD4 and clinical criteria) to monitor the children. There is increasing evidence that the routine CD4 and clinical monitoring, that are widely used, may not be sufficient to identify early enough patients who are failing on first line treatment. The development of viral resistance to a number of drugs poses a great danger and limits treatment options for the future (Sawe and McIntyre, 2009). On the other hand, using CD4 tests to determine failure may not be predictable and could result in premature switching to expensive second line treatment. Cost is cited as the main reason for not using routine viral

load testing, however the development of resistance and consequent second line treatment is a much higher price to pay.

This study was carried out to review patient records to see how the pediatric population at UTH was faring with regards to clinical outcome and CD4 profiles as predictors of viral load estimates.

CHAPTER 2

2.0 Literature Review

The 2010 WHO revised ART Guidelines in Infants and children recommends use of clinical, immunologic, or virological criteria to determine treatment failure and need to switch to second line therapy. The guidelines recognize the limitation in resource limited countries where there is the lack of routine viral load monitoring both at initiation and for routine monitoring. The current recommendations to switch to second line based on any three (clinical, immunological and virological) criteria are all conditional, clearly as a result of mounting evidence against reliability of clinical and immunological criteria as a marker of treatment failure versus the capacity to routinely carry out viral load testing. Viral load measurement is the accepted gold standard for monitoring treatment outcomes but has not been as widely used as CD4 testing because of cost. At $20 to $50 per test it costs four times more than the CD4 test (Reynolds, et al., 2009).

2.1 Evidence from Adult studies

Bagchiand colleagues (2006) demonstrated, in a retrospective longitudinal study including 466 subjects at the University of Alabama, neither clinical findings, nor CD4 counts are adequate predictors of viral suppression. A study from Botswana (Bisson, et al., 2006) also showed that CD4 cell count increase after initiating HAART has only a moderate ability to identify patients with undetectable viral loads. Similarly a study in Thailand (Chaiwarith, et al., 2007) reports that the sensitivities of using combined immunological and clinical criteria to determine antiretroviral failure (against gold standard of viral load measure) was extremely low at 20 percent.

Calmy and colleagues (2007) also argued that viral load testing may prevent unnecessary switching to second line therapy and the cost of not monitoring viral load testing is paid by complicated, costly and toxic regimes. A study from Uganda showed decisions to switch to second line therapy by an experienced HIV team, based on clinical and immunologic monitoring alone leads to unnecessary ART regimen changes in up to 35 percentof patients (Basenero et al., 2007). Furthermore, another study from Uganda, (Moore et al., 2008) showed that the use of CD4 count monitoring to identify patients who have not achieved virological suppression on ART can result in substantial misclassification of treatment responses with the danger of premature switching to second line therapy. A Medecins sans Frontieres study in Kigali, assessed viral load and CD4 response in 863 adults on ART for greater than one year. Using the WHO immunological criteria of failure as a decrease in CD4 to pre-therapy levels or $\geq$ 50 percent decrease in CD4 cell count from peak level, researchers found that 15.9 percent of patients would have been incorrectly started on second line treatment, while 8.8 percent would continue the first line regimen while having a detectable viral load (Van Greinsven et al., 2007). The conclusion was that WHO criteria perform poorly in predicting virological suppression.

The most recent evidence comes from two studies in Africa .A Ugandan study in which 1,133 men and women were followed up for three years. Overall viral load testing confirmed that 80 people (7.1 percent) were failing on treatment, the majority however were not detected using the standard CD4 tests. On the other hand CD4 testing alone identified 125 treatment failures; subsequently most of these (85 percent) were proven not to be failing by virologic monitoring (Reynolds et al., 2009). In Kenya a retrospective study identified 149 patients who had suspected treatment failure. Of these 58 percent turned out to still

have VL below 400 copies, who would otherwise have been misclassified and put on second line therapy (Kantor et al., 2009). These findings clearly show that following current WHO guides of clinical and immunological (CD4) monitoring wrongly identifies drug failures in infected people and misses a large number of infected people who are failing and need to switch to more potent second line treatment.

In his editorial comment in the Lancet (2006), Schooley pointed out that the benefits of antiretroviral therapy in resource limited settings is now clearly documented, however as we continue with further expansion of treatment programs, there is need to recognize the role of routine viral load testing and the danger of the consequences of treatment failure at individual and population level including the long term cost implications and drug resistance.

2.2 Studies in Children

Literature on virological response in children is limited to a few studies, in both developed and resource limited settings. In a US study (Rusteinet al., 2005), 263 children's clinical stage and CD4 were compared as predictors of viral suppression from baseline to one-year follow-up. This study concluded that near complete virological suppression was low and patients who were less likely to achieve virological suppression were those with AIDS defining illnesses, low CD4 counts or CD4 percent.

In another US study, Ding and colleagues demonstrated the challenges with adolescent populations (Ding et al., 2009). Of the 154 adolescents enrolled in the study, only 32.5 percent demonstrated early and sustained suppression at two consecutive follow up visits.

The remaining 67.5 percent had poor virological response either due to poor adherence or due to prior exposure to sub-optimal treatment.

Studies in children in resource limited settings have been restricted to clinical and CD4 outcomes as illustrated by studies in South African and Zambia (Janssen et al., 2010 and Bolton-Moore et al., 2007). Both these studies documented "good" clinical/immunological outcomes, but they were limited in their ability to measure corresponding viral load outcomes.

Where virological outcomes have been measured, the limitations have been short duration of follow-up, small numbers and young age of the children under study. In a retrospective cohort South African study (Reddi et al., 2007), 151 children initiated on HAART (median age at initiation 5.7 years) were followed for 12 months. Outcomes were measured by CD4 percent, weight gain and viral loads for 100 children that were available. This study reported increased CD4 by 16.2 percent from baseline, increased weight in 73 percent of patients within a month and viral load suppression at 12 months in 80.3 percent of the patients.

In 2007, Wamalwa et al.,followed up 67 Kenyan children (64 percent infants) over an average of nine months. HIV viral load, CD4 counts and z-score (weight for age and height for age) were measured. They reported significant overall increase in CD4 counts/CD4 percent, decreased viral loads and 67 percent viral suppression among the infants after 6 months of HAART. A similar study in Thailand (Puthanakit et al., 2005) involving 107 children (mean age 7.7 years) followed up for 72 weeks, reported significant improvement in CD4 percent, and z-scores (weight and height for age) as well as virological suppression in 76 percent of patients. A recent Zambian study under the CHAPAS group of research

showed 73 percent virological suppression in children with a median age of 6 yrs, followed for 48 weeks (Mulenga V, 2010). In another study in rural Zambia (Van Dijket al., 2011) 267 children followed up 24 months after initiating ART achieved good immunologic (88 percent had a CD4 T-cell percentage greater than 25 percent) and virologic outcomes (78 percent had an undetectable HIV viral load). These studies however did not compare the CD4 and clinical outcomes with the viral load measures.

Where closer monitoring using community based programs in Uganda (Chang et al.,2009) or directly observed treatment therapy, as in the Cambodian study (Sophanet al., 2010), were employed, the outcomes were promising (86 percent and 87 percent virological suppression respectively).

A more recent Ugandan retrospective study (Ruel et al., presented at the 2010 International Aids Society) commenced 117 children (mean age 4.8 years) on treatment and followed them up beyond 24 weeks. They were monitored closely using both CD4 and viral loads every 12 weeks. Of these 20 (17 percent) experienced sustained viremia beyond 24 weeks and only one child (5 percent) had a corresponding CD4 count that detected treatment failure according to WHO criteria. The rest of the 19 (95 percent) did not have a corresponding CD4 count to suspect treatment failure. In this closely monitored cohort, viral suppression rates were high 83 percent, but 19 out of 20 children with sustained viremia beyond 24 weeks were not detected using strict WHO CD4 criteria for treatment failure, clearly showing the need for virological monitoring in these settings. Similarly a Tanzanian study (Brathlomet al., 2010) reported widespread drug resistance among children

who received long-term (40 months mean) ART. 8 out of 19 children were virologically suppressed with only one child of the remaining 11 who were failing, experiencing a WHO stage IV event. All the 19 had a CD4 > 200cells/mm^3.

In children less than 2 years the CD4 percent are not a reliable marker for immune suppression and viral load estimations vary greatly, progression to severe immune suppression is rapid and effective treatment intervention to lower viral load early in life improves outcomes (Abram et al., 1996; Mphatsweet al., 2007; Davieset al., 2009). The most convincing evidence comes from the "Children with HIV Early Antiretroviral Therapy (CHER)" trial in which early HIV diagnosis and early antiretroviral therapy reduced infant mortality by 76 percent and HIV progression by 75 percent (Violari et al., 2008). Based on these studies, the WHO 2010 guidelines recommend that all children below 2 years should be commenced on treatment regardless of CD4 or viral load results.

2.3 Studies on adherence in children

Assessment of adherence, and support to ensure adherence, are always required when treatment failure is suspected. Several methods of measuring adherence in children have been used both in clinical settings and research. These include clinical staff judgment; self-reports (caregiver or patient); pharmacy records; pill counts; drug assays; electronic monitoring. Pediatric adherence studies show a varying range of reported adherence in children of all ages with no uniform measure across a number of studies. Adherence measures used in most studies are based on caregiver/parent or child/adolescent reports (missing at least one dose within the past 3 days or any dose in the last 3 months) and/or

pharmacy records. There are few studies that use reliable markers like plasma concentration of drugs (Albano F et al, 1999) or virological response to therapy (Van Dyke et al., 2002, Weiner Lori et al., 2004). Parents/patients often feel obliged to report higher levels of adherence to medical staff (Steele and Grauer, 2003).

A study done by Williams et al. (2006), followed over 2,000 children, for three years. Overall adherence was reported at 84 percent across all age groups; however, when comparing by age stratification, adherence was the worst (74 percent) in the 15-18 year age group. This was associated with high viral loads among the non-adherent group. In a review of literature derived from 13 studies in children, estimates of pediatric adherence were reported to range from 50 percent to 75 percent (Steele and Grauer, 2003). Another review of 32 pediatric studies revealed wide variations in measures and level of adherence with reported range of between 41 percent – 70 percent.

Feingold et al., (2000) studied adherence in 70 children on protease inhibitor therapy. They reported that 54 percent of the participants reported "good adherence" (missed less than 2 doses per week). Clearly there is a varying range of reported adherence in children of all ages with no uniform measure across these studies.

CHAPTER 3

3.0 Statement of the problem

Current literature has shown benefits of using viral load monitoring and the relative reliability of CD4 as a proxy to outcomes, however most of the **studies are limited to adult patients**, or if done in pediatric populations, **limited in terms of time of follow-up** since HAART initiation (6 months – Ruel T, 2010, Uganda; 12 months – Janssens B, Cambodia 2007; 9 months – Wamalwa DC, Kenya 2007) and the younger age of population of children under study (Wamalwa DC, 2007, 56 percent were infants; Ruel T, 2010mean age 4.8 yrs) Puthanakit Y, 2005, mean age 7.7 years; Janssesns B,2010, mean age 6 years).

The 2010 WHO Pediatric Guidelines (for resource poor countries) recommend use of targeted viral load (where available) **only toconfirm** clinical and or immunologic failure in children (also recommended at 6 months post ART initiation in children with Nevirapine (NVP) exposure who are initiated on NVP first line regimen to monitor response to therapy). However, regular plasma HIV viral load testing which is part of the standard of care for initiation and follow-up of HIV-infected children in the developed world is not routinely available in our setting. The South African Pediatric ART Guidelines are probably the only African guidelines that recommend use of viral load testing routinely at initiation of HAART and as part of routine monitoring (South African National Department of Health, 2010).

To wait for clinical and immunological failure before a viral load test, as evidenced from the literature above, **may in fact be a greater cost and further pull on the limited resources** in our setting. Hence, defining how best to use viral load and other monitoring approaches

to maximize efficacy and patient outcome is important to inform policy around use of targeted viral load or routine viral load in low resource countries.

3.1 Study Justification

Since September 2007, the laboratory capacity at UTH Department of pediatrics has improved and viral load testing is performed more routinely on a case-by-case basis as well as for patients who have been on HAART for 3 years or more. Six years into the program, over1000 patient samples had been tested, yet **no analysis had been done** on the levels of viral suppression, or the **relationship** between the viral load and routine parameters used (CD4 and clinical criteria) to monitor the children. There is **increasing evidence that the routine CD4 and clinical monitoring, that are widely used, may not be sufficient to identify patients** who are failing on first line treatment and may in fact pose a greater danger in the development of viral resistance to a number of drugs thus limiting treatment options for the future. On the other hand, using CD4 tests to determine failure may not be predictable and may in fact result in premature switching to expensive second line treatment. Cost is cited as the main reason for not using routine viral load testing, **however the cost of resistance and second line treatment is a much higher price to pay.**

Zambia is still debating about the feasibility of targeted versus routine viral load testing and cost is cited as one of the major barriers. **This study will help with the decision** on whether current parameters using CD4 and clinical findings are sufficient in identifying children who are failing first line therapy for targeted viral load testing or whether viral load testing should indeed be routine for all children commenced on HAART as argued by some

(Calmy et al., 2007; Schooley , 2006; Reynolds et al., 2009). It will add to the current pool of evidence on routine viral load testing versus CD4 and clinical monitoring.

Increased evidence on the critical need for virological testing will not only **add to the current pool** of knowledge, but may **increase the pressure and movement** calling for an increase in the access to viral load testing. With increased viral load testing sites, it can be assumed thatthe costs will decrease dramatically for all resource poor countries to access routine viral load tests. In addition, simple point of care viral load testing technology (Simple Amplification-based Assay), that can be used by clinicians outside the laboratory, is on the horizon and may make access to VL testing widespread (Lee et al., 2010)

This study will also provide a **basis for future studies** to compare the costs of long term incorrect treatment through switches and resistance versus cost of routine viral load testing. Increased evidence could result in increased use of viral load testing and development of simpler point-of-care tests.

3.2 Hypothesis

The study tested the hypotheses that CD4 count and clinical monitoring parameters were inadequate predictors of viral loads in children.

Null Hypothesis: Clinical and immunological monitoring were good predictors of viral load suppression in the pediatric population.

Alternate Hypothesis: Clinical and immunological monitoring poorly predicted viral suppressionin the pediatric population.

3.3 Objectives

General Objective: Review the clinical and immunological outcomes as predictors of virological response among children on HAART for more than 24 weeks at the University Teaching Hospital, Lusaka Zambia.

Specific Objectives:

- Prevalence of clinical, immunological and virological failure in children on HAART for more than 24 weeks at the UTH.
- To determine how well a patient'sclinical response and CD4 count **predicted** virological response for children on treatment for more than 24 weeks.

CHAPTER 4

4.0 Research Methodology

4.1 Definitions of Terms (Zambian Guidelines 2010)

Since the inception of the Pediatric ART program Zambian Guidelines for Antiretroviral Therapy of HIV infection in infants and Children (2007) have been developed. These are based on the WHO guidelines, but modified to suit the Zambian situation. In 2011 these guidelines were revised in line with the revised 2010 WHO guidelines. This study will use the definitions of failure as defined in the 2010 Zambian Guidelines for ART of HIV infection in infants and children.

Clinical Failure: In children on ART, the main clinical indications to switch therapy are the development of new or recurrent stage III or IV events (i.e., WHO Clinical Stage T3 or T4) at least 24 weeks after starting therapy with a first-line regimen (in a treatment adherent child)

Immunological Failure: Immunological failure is defined as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:

- In children below 2 years, the CD4 percent fall below 25% of the initial reading.
- For a child ≥2 years to <5 years of age, CD4 count of ≤200 cells/mm3 or percentCD4 fall to less than 15 percent or 50 percent fall from on-treatment peak or fall below the baseline CD4 count

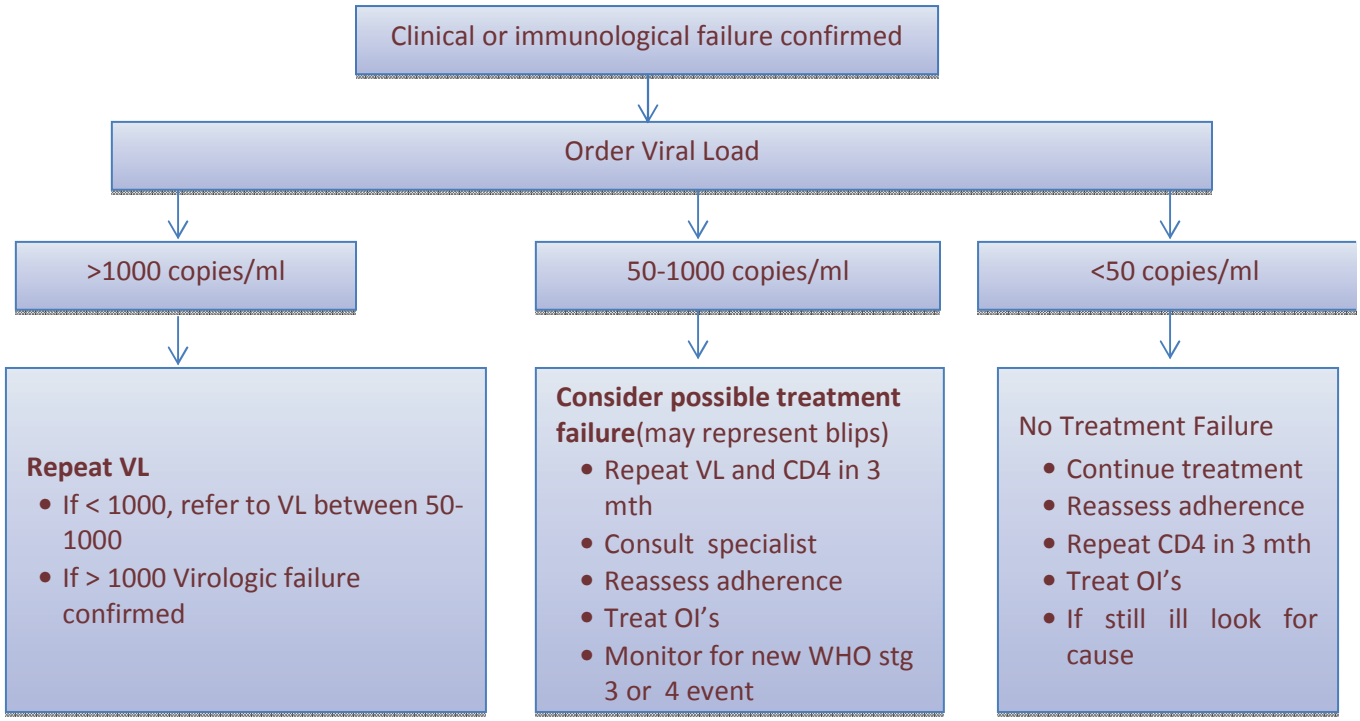
• For a child 5 years of age or older CD4 count of ≤200 cells/mm3 or 50 percent fall from on-treatment peak or fall below the baseline CD4 count

TABLE 1: Age-related Immunologic and Clinical Considerations to Switching to Second-line Therapy

Criteria	< 2 years of age	➢ 2years to < 5 yrs	➢ 5years
WHO staging	New stage 3 or 4 event (appearance or reappearance)		
CD4 percent	% CD4+ values fall to <25 percent	%CD4+ <15 percent	n/a
CD4 absolute count	n/a	• ≤200 cells/mm3 or • 50% fall from on-treatment peak or • Fall below the base line Cd4 count	≤200 cells/mm3 or 50 % fall from on-treatment peak or Fall below the base line Cd4 count

Virological failureis a persistent VL above 50 RNA copies/ml after at least 24 weeks on ART, in a treatment-adherent child. The availability of viral load is not a prerequisite for initiation of second line ART or for the determination of treatment failure.

Figure 1: Management of Patients with Possible Virological Treatment Failure



Children: This includes allchildren and adolescents in the age group between 0-19 years

Adherence: For the purpose of this study, adherence was measured by the routine care-giver or self-reported adherence data collected at every visit. Missed doses in the last 3 days, in the last month and since the last visit were collected but not used in the final analysis of this report.

Viral Blip: a single viral load result of 50-1000 c/ml, is not considered failure, repeat viral load should be performed in three months. For this study we considered virological failure as a reading of 1000 copies and above after at least 24 weeks of therapy.

Z-Score: The WHO Global Database on Child Growth and Malnutrition uses a Z-score cut-off point of <-2 SD (percentage below-2 SD from the reference median value).to classify low weight-for-age, low height-for-age and low weight-for-height as moderate and severe under nutrition, and <-3 SD to define severe under nutrition. The cut-off point of >+2 SD classifies high weight-for-height as overweight in children.

4.2 Study design

This study was a descriptive, non-intervention, retrospective chart review of routinely collected patient data from a cohort of HIV positive children and adolescents (both girls and boys), aged between 0 to 19 years, who had received ART for more than 24 weeks and had all the relevant clinical, immunological and virological information documented.

4.3 Study Population and sample size

This study was conducted at the UTH, department of Pediatrics and Child Health. Close to 4,000 children have been registered under the pediatric treatment program since September 2005. Of the 1,000 children, aged 19 or less, on the pediatric ART program from September 2005 to August 2010, who had available viral loads, a representative sample was calculated to include in the study for analysis of routinely collected data. A minimum sample size of 488 was calculated for representative analysis. We included 517 patients below age 19 years; with documented viral load results in the study (CD4 and clinical monitoring are done routinely every six months). The sample size calculation used is illustrated below:

Sample size calculation

Information on those with viral load tests performed was obtained from laboratory records and every second patient file was chosen in order of the date. Factors taken into account in calculating sample size were:

- Virological failure (gold standard) of 30 percent
- Pediatric Adherence rates of about 60 percent – so 40 percent poor adherence
- Poor records in 10 percent

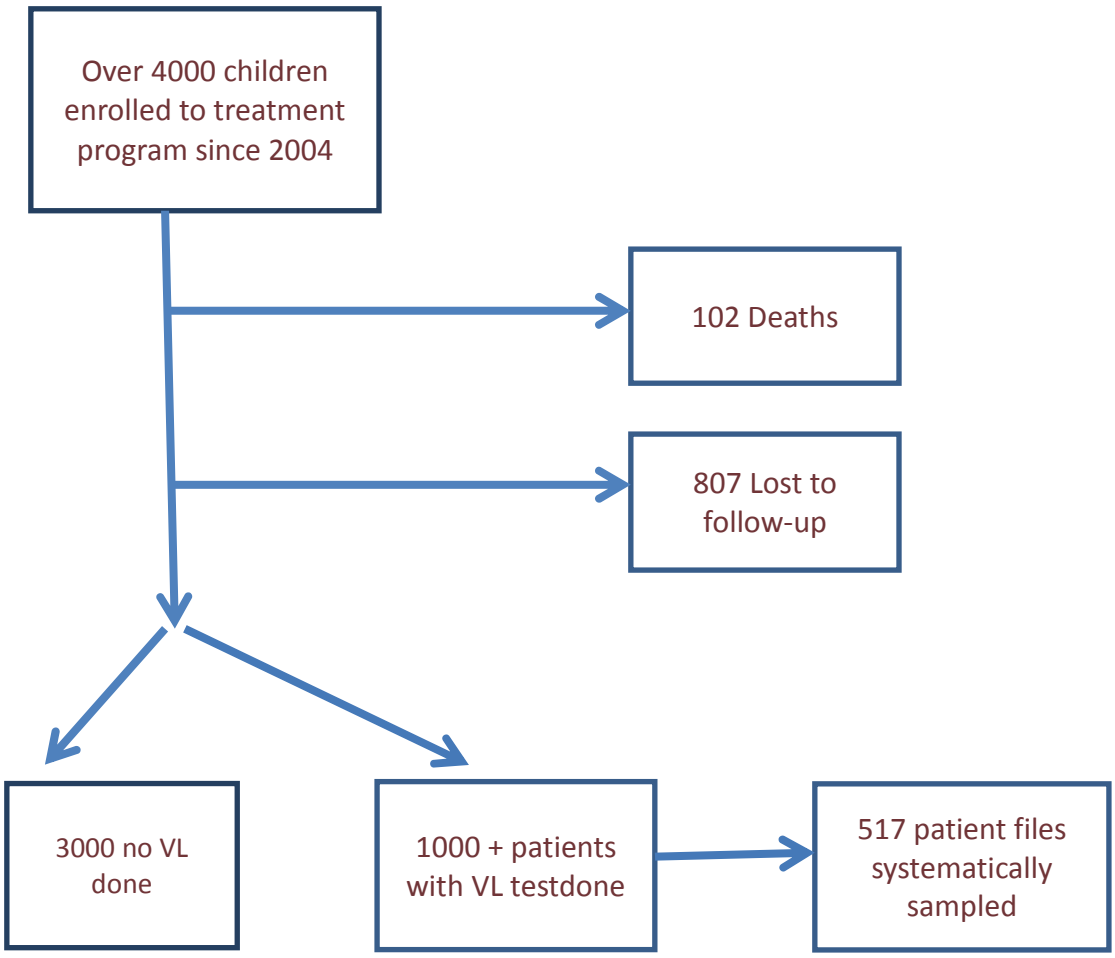
With these factors in mind, the formula used: $N= Z^2 p (1-p) / d^2$

- N= sample size, Z= 1.96 P= assumed proportions =30 percent d= 0,05 at 95 percent CI = 5 percent
- Population size =1000
- N = 244
- Apply the 60 percent poor adherence and 10 incomplete records: 244/0.5
- The required sample size = 488

A list of all the patients with available viral load testing was obtained from laboratory database. A computer generated list, in order of date of the viral load test, identified patients

using their hospital ART file numbers. For this analysis every second patient file from 1,000 records was conveniently sampled and selected for data collection. Were there was no ID or a missing file, the next patient in the sequence was selected. In general there were few missing files and the filing system at the Pediatric Centre of Excellence iswell organized making it easy to pull out records. A total of 517 patient records were included in this study and the flow of patients is depicted in the **figure 2** below.

Figure 2: Patient Flow Chart



4.4 Inclusion and Exclusion Criteria

Inclusion Criteria

- All pediatric patients between the ages of 0 to 19 years, who had been on ART for greater than 24 weeks and whose viral load results were documented were included for analysis.

Exclusion criteria

- Children on ART for less than 24 weeks
- Children with no previous record of viral load tests done in the file
- Files with poor correlation between timing of viral load, CD4 and clinical details

4.5 Study Instrument

A data collection form (see appendix I) was generated and filled out by research assistants from all the eligible patient files. The laboratory computer database was used to extract patients files according to the dates of Viral Load testing. Every second patient number was identified and file selected for inclusion in the study. Data collected included general and demographic information, details on ART initiation (clinical and immunological parameters, initial regimen), and details on viral load testing (dates, age, indication and switch to second line). Data was also collected on all subsequent six monthly visits including the routine clinical parameters, immunological data and all subsequent viral load tests up to the latest visit, last visit if patient no longer active at UTH or first five years of treatment if patient has been longer on treatment. Outcome data on the patients in the study were also collected (hospitalization, transfer, death or still on the UTH-PCOE program). In the majority of patients, clinical visits and labs correlated well with the six monthly visits. However where they did not correlate well the nearest visit plus or minus 2 months were aligned with the laboratory test results.

4.6 Data collection

Clinical and laboratory data was transcribed on to a data collection form using patient records. All the data collection forms were given a unique study number to remove any patient identifiers. Eligible patient files from September 2005 to August 2011 were included in the study. Data collection spanned a 3 month period from Sep to Nov 2011. All data was entered (double entry) onto computer software using Microsoft Access 2010 database. The analysis was done in SPSS version 18.0 analytical program.

For ease of data management, entry, validation, analysis and reporting, the principle investigator collected completed forms weekly checked them for completion and passed them on for data entry by 2 independent data entry clerks. All data entry was supervised by the Data Specialist from the Pediatric Centre of Excellence. Data was cleaned and analyzed by the principle investigator with the help of supervisors and data manager at PCOE. All Questionnaires with patient information were kept in a locked filed cabinet and electronic files were encrypted with password protection.

4.7 Data analysis

Data from the collection form was double entered into a Microsoft Access file and analyzed using SPSS version 18.0. The analysis includes basic descriptive and demographic data, presented as numbers and percentages Univariate analysis of variables like demographics, initial clinical and laboratory parameters and viral load results after >24 weeks of treatment was done to determine the distribution patterns. Simple linear regression was used to see how well the independent factors could predict VL failure. Multivariable regression analysis was used to examine the linear correlations between independent variables and the

dependent variable (Viral Load). Pearson's correlation coefficient was used to estimate as to degree of association and the coefficient of determination (100 R^2 model) was used to determine prediction of future outcomes using these data.

Dependent Variable: Viral load result

Independent variables: Demographic characteristics including age, sex, residence, length of treatment; Laboratory parameters like CD4 count and hemoglobin as well as clinical elements including WHO clinical stage and BMI Z-score. Patient CD4 and clinical staging data were collected for every six month visit. All available viral load results during these visits were recorded. For the majority of patients this was a one off viral load test done during the course of treatment, particularly around 3 years of therapy. Care-giver or self-reported adherence forms that are routinely filled out at every visit were also recorded at each six month period. Levels of adherence (missed doses in the last three days or since last visit were used to see how they compare with the CD4 and viral load trends. The study compared the following:

- Clinical outcomes using WHO criteria, Hemoglobin and BMI Z-score were compared with viral load reading at the time first viral load was done.
- Age related CD4 percent /CD4 count versus viral load monitoring as a marker of immune function and disease progression
- Virological outcomes at 3 years and 5 years of treatment were also analyzed
- Simple linear regression and multiple linearregression were used to see what the relationship was between independent variables (clinical and immunological)and the dependent VL reading.

All analysis was considered statistically significant at 95 percent confidence interval and a p-value of less than 0.05.

4.7.1 Data quality control

Prior to the study, research assistants and data entry clerks were trained in a one day session to orient them on the following: study background, terms and procedures to be followed, ethical issues and maintaining confidentiality of all patient records. The data collection form was pre-tested and refined before the actual study. All forms were checked weekly for consistency and completeness of data by the principle investigator before entry on computer by the data clerks.

4.7.2 Ethical considerations

Approval to carry out this study was sought from the University Teaching Hospital management and UNZA Biomedical Research Ethics Committee. Changes to the protocol during the course of the study included: inclusion of all patients aged 0-19 years and change in the sample size – calculated sample size rather than all the available files. Sample size calculation was used to arrive at a minimum on 488 patient records for inclusion. All changes to the protocol were approved by the Biomedical Research Ethics Committee.

All information collected from patient files, computer records and laboratory records were kept in a locked cupboard. No patient identifiers were used and no patient interaction was embarked on. This is a retrospective record review with routinely collected information from records of visits over a maximum of 5 years.

4.8 Confidentiality

Data collected on the form did not include subject names. The form included the patient hospital ID number (unique ART number) so that files could be traced to abstract patient information regarding treatment. Each questionnaire was allocated a unique study number by the research assistants.

During data cleaning, the unique study number was used to trace back to individual forms and subsequently UTH file records when the need rose to check any further missing details. Completed forms were retrieved by the principle investigator and have been stored in locked file cabinets. All data entered onto computers are password protected.

CHAPTER 5

5.0 RESULTS

5.1 Social-demographiccharacteristics of the Patients

A total of 517 patients were included in the study (as they met the criteria of at least one Viral Load done after 24 weeks of treatment). Highlights of baseline characteristics are presented in **Table 2**below**.**Treatment was started from UTH in 97 percentof the patients. The majority (who had documented CD4/Staging) had advanced disease at enrollment with 74percent(384/501)eligible for treatment at first contact based on CD4 or WHO clinical criteria. Of the 118 not eligible for treatment at enrollment, 52 percent were starting/completing TB treatment, 34 percent still had high CD4 counts and were clinically not eligible and 14 percent had no clear reason for not starting treatment.Children starting treatment in the adolescents' age group (10-19 years) accounted for 31 percent of all patients. Clinical staging and immunological monitoring at initiation of ART was documented in 95 percentand 93% of the patients respectively. The majority, 78 percent, were in clinical stage III and IV and 73 percent were immunologically failing at initiation.

Looking at rates of admissions after ART initiation, a total of 71 (14 percent) patients were admitted at least once after initiating treatment. The commonest reason for the first admission was pneumonia (6 percent). Malaria and malnutrition contributed to 2 percent each for these admissions. A total of 168 (32 percent) were switched to second line treatment in the five year (or less) of follow up period. The decision to switch was based mainly on VL (73 percent) with clinical and/or immunological criteria supporting this switch in 26 percent of patients. Of all 517 patients, the initial VL results after 24 weeks or

more of treatment showed that 60 percent had a VL below 1000 (well suppressed), while 40 percent had a VL above 1,000, indicating failure after at least 24 weeks of therapy.

TABLE 2: Baseline characteristics of Children on HAART at the UTH PCOE

Baseline Characteristic	Value
Demographics/Social	
All patients	517
Female percent	48 %
Median Age at ART initiation (SD 4.7 yrs)	7 years (range 3 – 11)
Orphaned (n=233)	45%
Primary Caregiver of child mother or father	70 %
Clinical/immunological at initiation	
Clinical Stage done at initiation (n=491)	95 %
III and IV	78 %
Initial BMI Z-score -2 or less	30 %
Initial hemoglobin (mean/range)	10 (4 – 21)g/dl
CD4 documented at initiation (n= 482)	93%
CD4 %< 25% for children less than 2 yrs. at initiation (n=100)	88%
CD4 % < 15 in children between 2 – 5 yrs (n=93)	67%
CD4 count < 350 in children above 5 years (n=289)	70 %
CPT prophylaxis at or before initiation	84 %
TB treatment at enrollment/initiation	13.5 %
Eligible for ART initiation at enrollment	74 % (284/501)
Viral Load	
Initial Viral Load test - mean time after initiation	33 months (2.7 yrs; SD 1.5 yrs)
Initial VL test result above 1,000	40 %
Antiretroviral treatment : Initial ART drug choice	
AZT/3TC/NVP or EFV	44 %
D4T/3TC/NVP or EFV	52 %
Switch to second-line (n=168)	32 %
Reason for switch based on VL	73 %
Outcome (percent)	
Active on treatment (up to July 2011)	91 %
Outcome of those not active (n=47)	
Transferred Out	19 %
Lost to follow up	70 %
Died	11 %

The common second line treatment regimens were: ABC/3TC/LPV/r (39 percent) Ddi/ABC/LPV/r (35 percent) and Truvada based regimen in 20 percent of patients. As of November 2011, Didanosine (Ddi) had been completely phased out and patients put on suitable alternatives.

Outcome data shows that 91 percent of patients were with the UTH PCOE program by 31st July 2011. Only 9 percent (47) were no longer with the UTH program, majority of whom were lost to follow-up (70%).

5.2 Prevalence of clinical failure

Table 3: Prevalence of Clinical Failure:WHO Staging at the time first viral load was done

	Viral Load (copies per ml)		
	Below 1000	Above 1000	Total
WHO Stage I and II	210	149	359
	58.5%	41.5%	
WHO Stage III and IV	78	45	123
(severe immune suppression)	63.4%	36.6%	
Total	288	194	482
	59.8%	40.2%	

Table 3 shows that a total of 482 patients had WHO staging done at the time first VL test was done. Of the 359 patients with a clinical stage I or II (not severely immunosuppressed), 41 percent were failing virologically. These show quite anlarge number of patients who seemed to be doing fine on WHO clinical staging, were failing virologically. On the other hand, 63 percent of the patients with poor clinical picture (clinically severely

immunosuppressed); had a viral load below 1,000. Again a large number of patients were clinically doing poorly, but when the viral load was done, it was actually well suppressed.

Table 4: Prevalence of Clinical Failure:Hemoglobinlevels at the time first viral load was done

	Viral Load (copies per ml)		
	Above 1000	Below 1000	Total
Hemoglobin level below 8g/dl	10	3	13
	75.9%	23.1%	
Hemoglobin level 8g/dl and above	290	201	491
	59.1%	40.9%	
Total	300	204	504
	59.5	40.5	

Table 4 shows that very few patients had hemoglobin (Hb) below 8g/dl at the time the first viral load was done. Majority of the patients (95 percent) had an Hb above 8g/dl at the time the first viral load test. Of these 41 percent had a viral load above 1000, indicating that despite a good Hb they were actually failing.

Table 5: Prevalence of Clinical Failure:BMI Z-Score at the time first viral load was done

	Viral Load (copies per ml)		
	Below 1000	Above 1000	Total
BMI -2 or less	44	33	77
(moderate to severe malnutrition)	57.1%	42.9%	
BMI -1 and above	258	171	429
	60.1%	39.9%	
Total	302	204	506
	59.7%	40.3%	

Table 5 shows that 506 patients had a BMI Z-score reading at the time first VL was done. Of the 77 patients that had a BMI Z-score -2 or less (indicating moderate to severe malnutrition) at the time first VL was done 57 percent of them had a VL below 1000 (virally well suppressed). Interpreting this shows that a high percentage of patients who are not doing well nutritionally can actually be well suppressed virologically. Further, of the 429 who had a BMI Z-score of -1 and above (nutritionally well) 40 percent were failing virologically. This again highlights the unreliable nature of monitoring using clinical parameters.

5.3Prevalence of Immunological Failure

Table 6: Prevalence of immunological Failure at the time first viral load test done

	Viral Load (copies per ml)		
	Below 1000	Above 1000	Total
Immunological failure	30	76	106
	28.3%	71.7%	
Immunologically fine	273	130	403
	67.7%	32.3%	
Total	303	206	509
	59.5%	40.5%	

Table 6 shows that there were 509 patients who had an immunological staging done at the time first VL was done. Of the 106 patients who were failing immunologically, 28 percent were virologically well suppressed. On the other hand of the 403 who were immunologically doing fine, 32 percentwere virologically failing, again raising the question on how reliable immunological monitoring is for patients on ART.

5.4 Prevalence of Virological Failure

The prevalence of virological failure at the time that first VL was done was 40 percent. Self-reported adherence data though captured in the data collection form, were not taken into account in this analysis.The table below (table 7) shows the frequency of VL tests performed at each six month time-point and also gives an idea of the indication for the test – whether routine or indicated as a result of clinical or immunological criteria.

Table 7: VL tests done at each six-month time point; Failure rates among those who had a VL test and Indication for VL test

VL after ART initiation in Months	Total patients still on program	Total # VL tests	VL Failure (above 1000)	Routine Indication	Clinical/CD4 Indication	VL done while on second line
Viral Load at 6 months (24 weeks)	517	22	5 (22 %)	14 (64 %)	8 (36 %)	0
Viral Load 12	514	55	28 (51 %)	22 (40 %)	33 (60 %)	0
Viral Load 18	507	79	40 (51 %)	13 (16 %)	47 (59 %)	1 (1 %)
Viral Load 24	488	88	32 (36 %)	38 (43 %)	41 (47 %)	9 (10 %)
Viral Load 30	458	106	41 (39 %)	68 (64 %)	29 (27 %)	9 (8 %)
Viral Load 36	**399**	**141**	**57 (40 %)**	**87 (62 %)**	**37 (26 %)**	**17 (12 %)**
Viral Load 42	346	107	50 (47 %)	63 (59 %)	32 (30 %)	12 (11 %)
Viral Load 48	238	83	31(37 %)	44 (53 %)	24 (29 %)	15 (18 %)
Viral Load 54	217	81	35 (43 %)	44 (54 %)	15 (34 %)	22 (27 %)
Viral Load 60	**172**	**88**	**33 (37.5)**	**47 (53 %)**	**16 (18 %)**	**25 (28 %)**

Table 7 shows the number of VL tests done at each six month time-point. Some patients had multiple VL tests done over the years. Of note is that at **3 years (36 months)** of treatment, there were still 399 patients being followed up. 141 patients had a VL test done and 40 percent were failing (either on first or second line of therapy). The majority had a routine indication for VL test (64percent). A more detailed look at this time point showed 124 of the patients were still on first line treatment with 40percent (50/124)failing on their first regime. Of the 17 on second line treatment, 7 patients were still failing virologically.

A further analysis at the **5 year (60 month)** time point showed that there were 172 patients still on treatment. Of these, 88 patients (51 percent) had a VL test done with nearly half (53 percent) having a routine indication for the test. From the 88 with VL done, 63 (72 percent) were still on first line drugs with 59 percent (37/63) well suppressed and 41 percent (26/63) failing on first line at 60 months of treatment. Of the remaining 25 (25/88) who were on second line by 60 months of treatment, a further 6 were failing on their second line drugs.

5.5 Clinical and Immunological parameters as predictors of VL

Table 8: Assessing how well BMI, Hb, WHO and Immunological status can predict VL individually

	VL Failure	VL Suppressed	Total	Odds Ratio	Significance	95% C.I.	
Variable						**Lower**	**Upper**
Immunological Status	206	303	509	0.326	0,01	-0.494	-0.295
Hemoglobin	204	300	504	0.058	>0.05	0.092	0.450
WHO Staging	194	288	482	0.044	>0.05	-0.150	0.052
BMI	204	302	506	0.019	>0.05	-0.268	0.152

Simple linear regression results **(table 8)** shows that Hb, BMI, WHO Staging on their own are not good VL failure predictors

- B=.179, df(501)=1.67, **p>.05**, r=.058 (Hb)
- B=-.049, df(479)=.920, p>.05, r=-.044 (WHO Staging)
- B=-.049, df(503)=.189, **p>.05,**r=-.019 (BMI)

However immunological status did have significance in predicting VL failure

- B=-.394, df(506)=60.4, **p<.01**, r= -.326 and 95percentCI [-0.49 to -.29]
- $100R^2$ = coefficient of determination – used to predict future outcomes on basis of related information
- **100R-Squared**=10.6 shows that the model with CD4 could only predict 10.6 percent

Can a combination of factors help improve VL failure detection? All variables were combined in the multiple linear regression equation. Results presented in **table 9**below.

Table 9: Multiple Linear Regression using all the variables

	Odds Ratio	**Significance**	**95% C.I.**	
Variable			**Lower**	**Upper**
Immunological Status	0.172	0.000	1.101	0.292
Hemoglobin	1.961	0.480	0.302	12.720
WHO Staging	0.873	0.561	0.553	1.380
BMI	1.119	0.830	0.403	3.107
Constant	7.997	0.156		

100R Squared =13.8

Multiple linear regression was conducted to assess whether the four predictor variables significantly predicted the patient failing virologically

- A significant result was obtained $X^2=49.93,df=4,N=464,p<.001$
- **Only immunological status is contributing to the VL failure prediction**
- **Table 9** above shows that the odds of failing virologically reduces as the CD4 increases

5.6 Prediction of VL failure using all the variables in Multiple linear regression

- Model summary estimates R-Squared (coefficient of determination that predicts outcomes or percent of variance)
- Therefore, the model can predicted 13.8 percent of virological failure with all four factors taken in to account (Hb, BMI Z-Score, WHO staging and CD4)

5.7 Immunological status as predictor of VL failure but how well?

Table 10: percent predicted using CD4 by the model

Observed	Predicted Viral Load		
	VL below 1000	**VL above 1000**	**Percent correct**
VL below 1000	254	23	91.7
VL above 1000	123	64	34.2
Overall percent			68.5

Table 10shows that using CD4/immunological criteria, the overall prediction of VL is 68.5 percent. Separating this according to VL above or below 1000, we see that 91.7 percent of those who had a viral load below 1000 were correctly predicted, **but for those who had a VL above 1000, only 34.2 percent were predicted correctly.**

CHAPTER 6

6.0 DISCUSSION

This review of pediatric ART program at the UTH shows that clinical and immunological monitoring, the predominant practice in our setting, are not reliable markers of virological response. Biologically, virological failure occurs earlier, followed by immunological failure then clinical failure. Diagnostically the reverse is true in resource limited settings (Kantor et al, 2009) due to laboratory constraints. Finding the best monitoring modality without the use of viral load testing has been a challenge.

The clinical parameters used in this study (WHO staging, Hemoglobin and BMI Z-score) were not good predictors of VL failure. Most studies in literature that have used varied clinical markers show that these are not reliable for monitoring patients. This is evidenced from a study by Bagchi et al (2006) in a retrospective longitudinal study involving 466 subjects, where clinical markers used included hemoglobin, platelet count, percent change in total lymphocyte count and weight gain in first three months of therapy. Neither of the clinical markers, alone or in combination, could predict virological response. Studies by Janssen et al., 2010 and Bolton-Moore et al., 2007 showed that clinical markers (WHO staging and Hb– Janssen et al., 2010), weight gain and Hb (Bolton et al., 2007) improved significantly in children on ART, however these two studies were limited in their ability to monitor against gold standard of VL testing.

Immunological criteria in this study did have a significant prediction on virological failure, ($p<.01$, $r= -.326$ and 95percent CI [-0.49 to -.29], however when size effect taken into account; this prediction was low,10.6 percent. Further the percent predicted using CD4

shows that overall prediction was 68.5 percent, but for those that are failing virologically this prediction was at a low 34.2 percent. Studies on the sensitivity and specificity of combined clinical and immunological criteria to predict failure were 20.0 percent and85.9 percent respectively (Chaiwarith et al., 2007). Looking at immunological criteria alone in adults, Kantor et al (2009) found that 58 percent of patients would have been switched prematurely to second line therapy based on CD4 criteria alone. Similarly, Moore et al., (2008) concluded that CD4 cell monitoring does not accurately identify individuals with virologic failure among patients taking ART.

In a more recent closely monitored cohort of 300 HIV infected children in Uganda (Ruel et al., 2010) viral suppression rates were high (83 percent) beyond 24 weeks of therapy, however, 19 out of 20 children with sustained viremia were not detected using age related CD4 criteria for treatment failure. The authors conclude that virological monitoring is needed to alert clinicians on the need for adherence counseling and prevent the development of ART resistance. Another study in Tanzania (Bratholm et al., 2010) that followed up a much smaller number of children who had been on treatment for a longer period (median three years three months) found that 11 out of 19 children were virologically failing. In spite of this widespread failure, only one child was failing clinically and none had CD4 criteria to suspect treatment failure. A study by Mee et al. (2008) showed that WHO clinical and immunological criteria poorly predict virologic failure after 1- year treatment in South Africa, where viral load testing is available. All these are in support of our findingsat UTH.

This study clearly shows that though CD criteria may have some benefit in helping to classify treatment failure (68.5 percent prediction), the benefit is largely for those who are

doing well anyway. For a large number who have seemingly good CD4 outcomes, the high underlying viral load readings bring to question the benefit of relying on CD monitoring.

The virological failure rates in children in this study are high (40 percent) beyond 24 weeks of therapy (40 percent at 36 months and 41 percent by 60 months for those still on first line). This is most likely as a result of treatment failure due to reduction in ART effectiveness, poor adherence, development of drug resistance and lower potency regimens or a combination of factors. Similar reports in children with long term follow-up have been made. Song et al. (2007), in a study in Kenya showed that 45 percent of children were still not suppressed virologically after 9 months of treatment. Bratholm followed up 19 children in a Tanzanian study with VL results for a median of 40 months and found that 58 percent were failing on treatment. The numbers with VL results in this Tanzanian study were small, but few studies have assessed long term follow up in children. Other studies showed better outcomes; at 12 month follow up of 100 children who had VL tests done in South Africa, 80 percent were well suppressed. Davies et al (2009) reported excellent treatment outcomes in a large pediatric multicenter cohort in South Africa. 82.4 percent of the children were well suppressed virologically after 3 years on ART.

Adult virological failure rates after long term therapy in many studies are much lower than this: 15percent in a Tanzanian study (Brathlom et al., 2010); 16.4percent (Moore etal., 2008) in a Ugandan study and 7.1 percent in a study that followed up patients for three years (Reynolds et al., 2009).

The findings from our study, in conjunction with the current literature from pediatric studies in resource limited settings, clearly show that clinical and immunological monitoring are not the optimal modality for monitoring patients on HAART. There is need to reconsider

current WHO guidance taking into account financial and infrastructure constraints. This may be in the form of selective viralogical monitoring using CD4 cell percent changes (Kantor et al., 2009) or consideration of simple point of care VL testing currently on the horizon (Lee H et al., 2010).

This study looked at a number of variables, and further analysis will be carried out on the relationship between reported adherence rates and VL failure as well as stratification by adolescent age group and indication for VL testing (routine versus clinical or immunological indication). These analyses may shed more light on the outcomes reported so far.

This study is valuable because of the large number of children included in the analysis, the length of follow-up (median age of VL done after 2.7 years) of up to five years of treatment and the available viral load results for all these children. Few studies have regular HIV viral load information in the African context, particularly in children.

6.1 Limitations of study

This was a hospital-based study design and so data was collected only of children who were on the treatment program at University Teaching Hospital. Children included in the study were only those who had viral load testing done at some point during treatment (> 24 weeks). The findings may not be generalizable, however they will add to the pool of existing data from adult studies and this is one of very few studies which actually address children where viral load testing is used asa gold standard. This study did not address adherence issues in relation to failure nor did we address the adolescent population who made up 31 percent (161) of all patients and may well have contributed significantly to high level of treatment failure.

CHAPTER 7

7.0 CONCLUSIONS AND RECOMMENDATIONS

This study, like many others that have been done in adults, shows that clinical parameters were not good predictors of VL failure. In this study, immunological criteria did have a significant prediction on virological failure, BUT when prediction models were used and size effect taken into account, this prediction is low, especially for those who are failing and have viral load above 1,000 copies. The implication is that CD4 monitoring can easily miss out those that are failing virologically with resultant multiple drug resistance mutations and increased cost of second line therapy.

RECOMMENDATIONS

1. There is need to advocate and move forward with routine VL testing in Zambia for an efficacious monitoring of ART programs.
2. The additional data variables collected for this study need to be analyzed further to shed more light on the outcomes reported so far.
3. More research is needed on the long term outcomes of HAART in children where the gold standard of viral load is used for monitoring treatment outcomes and where follow up is beyond 36 months.

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