IMMUNOLOGICAL RESPONSE TO ANTIRETROVIRAL TREATMENT AFTER EXPOSURE TO ZIDOVUDINE OR SINGLE DOSE NEVIRAPINE PROPHYLAXIS FOR PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV IN DAR ES SALAAM

By

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A dissertation Submitted in (partial) Fulfillment of the Requirement for the Degree of Master of Medicine (Obstetrics and Gynecology) of the Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certifies that he has read and hereby recommends for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation entitled ***"Response to Antiretroviral Treatment after exposure to Zidovudine or single dose Nevirapine prophylaxis for Prevention of Mother to Child Transmission of HIV in Dar Es Salaam"***, in (Partial) fulfilment of the requirements for the degree of Master of Medicine in Obstetrics and Gynaecology of the Muhimbili University of Health and Allied Sciences.

……**.....**……..

Dr. Charles Kilewo

(Supervisor)

…….

Date

DECLARATION AND COPYRIGHT

I, **Dr. Mussa K. Msemo**, declare that this**dissertation**ismyoriginal work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature …….. Date ……..

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DEDICATION

I dedicate this dissertation to my wife Magdalena Haule for her endurance during my residence training.

ABSTRACT

Background:

Mother to child transmission (MTCT) of Human Immunodeficiency Virus (HIV) causes about 90% of newly infected infants and children. The risk MTCT of HIV without intervention ranges from 25 to 40% if breastfeeding is continued for two years. The use of antiretroviral (ARV) drugs for prophylaxis during pregnancycan reduce the transmission significantly. The use of sdNVPor any other short regimens containing one or two drugs however induces viral resistance and can lead to treatment failure when a woman subsequently starts ART for her health.

Objective:

To assess the immunological response to Antiretroviral treatment of immuno-suppressed women previously exposed to Zidovudine or single dose Nevirapine prophylaxis for prevention of mother to child transmission of human immunodeficiency virus in Dar es salaam.

Method:

A retrospectiveCohort study was conducted in four CTC – clinics in public hospitals, in Dar es Salaam from July 2012 to October 2012.Women currently on ART but previously exposed to ARV prophylaxis for PMTCT were compared to unexposed (naïve) women also on ART and determined the immunologic response.Semi structured questionnaire was used to collect social demographic characteristics information. Data management was done using the SPSS statistical program version 16.0.

Results

A total of 807 clients were analyzed, whereby 288 were exposed to either ZDV or sdNVP. Median CD4+ counts of exposed and unexposed were not comparable at baseline whereby there was statistical difference, as exposed group had higher median CD4+ counts 163 (IQR 89-206) as compared to the unexposed 124 (IQR 63-192) (p-value 0.000). At six months and twelve months the Median CD4+ counts changed the trend whereby the unexposed had slightly higher CD4+ counts as compared to exposed, although they were not statistically significant, (p-values 0.383 and 0.971 respectively). There was increase in median CD4+ counts of +70 and +164 cell/µl at six and twelve

months of ART respectively in Exposed group, while in unexposed group the change was +126 and +196 cells/µl. These changes are with respect to the baseline CD4+ cells counts.

At six months 12.5% of women who were exposed had Immunological failure while only 4.2% of unexposed had immunological failure, which was statistically significant (0.000), and had three times higher chance of developing failure CI (1.86-5.60).

Conclusion

At baseline, six and twelve months of initiation of ART the statistical significant difference in CD4+ cell count levels was not observed among women exposed to the PMTCT prophylaxis and those who were unexposed.When immunological failure checked as per exposure the findings were statistically significant. Initiation of ART, within six months post exposure, contributed to the poorer CD4+ response significantly as well as immunological failure as compared to those who initiated beyond six months.

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LIST OF ABREVIATIONS

3TC:	Lamivudine
AIDS:	Acquired Immune Deficiency Syndrome
ARV:	AntiRetroViral
AZT:	Azidothiamidine
cART:	Combination Anti-Retro Viral Therapy
CD4:	Cluster of differentiation
CTC:	Care and Treatment Clinic
d4T:	Stavudine
HAART:	Highly Active Anti-Retroviral Therapy
HIV:	Human Immune deficiency Virus
IQR:	Inter-quartile range
MDH:	Management Development for Health
MNH:	Muhimbili National Hospital
MTCT:	Mother to child transmission of HIV
NACP:	National Aids Control Program
NNRTI:	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI:	Nucleoside Reverse Transcriptase Inhibitors
PI:	Protease Inhibitors
PMTCT:	Prevention of Mother to Child Transmission of HIV
RCH:	Reproductive and Child Health
s.d:	standard deviation
sdNVP:	single dose Nevirapine
TDF:	Tenofovir
UN:	United Nations
UNAID:	The Joint United NationsProgramme on HIV and AIDS
WHO:	World Health Organisation
ZDV:	Zidovudine

DEFINITION OF TERMS

Immunological response: successfully immunological response is an increase in CD4 cell count of > or =50 cells/microL over the baseline value after commencing HAART

Immunological failure:defined as a 50% drop in CD4 count from peak value within 6 months, or return to pre-ART baseline CD4 count or lower.

In this study the immunological failure was checked at six and twelve months respectively by identifying those whose CD4+ cell counts did not rise or dropped to or below the baseline.

Poor adherence: Taking ARV less than 95% of all the time while on HAART. (Were referred from ARV adherence forms)

Option B+

Provide all HIV-positive pregnant or breastfeeding women with a course of triple antiretroviral drugs to prevent mother-to-child transmission and continued for life regardless of CD4 count or clinical stage.

Option B

Provide all HIV-positive pregnant or breastfeeding women with a course of triple antiretroviral drugs to prevent mother-to-child transmission. A triple-drug antiretroviral regimen should be taken throughout pregnancy and delivery. If the mother is breastfeeding, she should also continue to take the triple-drug antiretroviral regimen until 1 week after breastfeeding has finished.

Pregnant women who are eligible to receive antiretroviral treatment for their own health, based on their CD4 count or clinical stage, should continue taking HIV treatment for life.

BACKGROUND

Acquired Immunodeficiency Syndrome (AIDS) epidemichas affected sub-Saharan Africa region than any other region of the globe, more than 68% of infected people reside.About 1.9 million people were newly infected with HIV in 2010, bringing to 22.9 million the total number of people living with the virus. Unlike other regions, the majority of people living with HIV in sub-Saharan Africa 59% are women[1].

Mother to child transmission (MTCT) of Human Immunodeficiency Virus (HIV) is the major cause toabout 90% of newly infected infants and young children.Estimates of about 1.4 million people areliving with HIV in Tanzania; most of them are adults. The national HIV prevalence rate among adults of reproductive years is 5%[2]. The risk of Mother to child transmission (MTCT) of HIV without intervention ranges from 25 to 40%if breastfeeding continues for two years[3]. Risk of transmission is highest during labor and delivery.

Studies conducted in resource limited countries have demonstrated that using mono ARV drug regime for prophylaxis treatment initiated either antenatally or in the intrapartum period can result in significant reduction in transmission of HIV-l from mother to infant. These short course PMTCT regimens have therefore been introduced in Tanzania and other resource limited countries from 2000 to date. These short course regimens for PMTCT have a major impact on controlling perinatally acquired HIV infection [4].

The presence of ARV therapy can alter viral ecology if the therapy allows ongoing viral replication; drug-resistant variants may become selected as long as the drug is administered. There has been some concern however that the use of ARV monotherapy for the prevention of MTCT, including Zidovudine (ZDV) or single dose Nevirapine (sdNVP) could result in the development of drug resistance with potential implications for the choice of therapy for the HIV-infected infant and future maternal therapeutic options[5].

Tanzania’s health facilities with RCH services which offer PMTCT services are about 93%[6]. In the year 2010, the RCH facilities tested up to 81% of pregnant women who attended antenatal clinics. Pregnant women who tested positive for HIV 93%

received prophylaxis[1]. This number is only 71% of all HIV infected pregnant women.About 50% of deliveries in Tanzania occur at home[7]. Single dose Nevirapine(sdNVP)was therefore the main prophylactic medicine offered [6, 8].

Detection of Zidovudine or Nevirapine resistance was reported not associated with increased risk of vertical transmission. Various studies have demonstrated that the treatment failure is increased when such exposed women subsequently start first line Highly Active Anti-Retroviral Therapy (HAART) [9, 10].

The Risk of altered virological and immunological response is more particularly when Non-Nucleoside Reverse Transcriptase Inhibitors are initiated within six months after delivery [11-13].

Globally, the prevalence of treatment failure occurs is 30% of the patients on HAART [14]. This prevalence varies between continents. North America reported prevalence of 12 %[15]while Uganda reported the prevalence of immunological failure of 38%[16]. HIV/AIDS patients in Tanzania and other countries in Sub-Saharan Africa are also at higher risk to develop treatment failure due to poor adherence, which constitutes a serious challenge to those receiving ART [17, 18].

The adherence of more than 95% is associated with viral load suppression of 81%; however, 90-95% adherence will be associated with viral suppression of 64%. The 80-90% adherence will be associated with suppression of 25% and adherence of less than 70% will suppress only 6% [19]. To be successful, ART medications must be taken at least 95 % of all the time the individual is taking medicine [20]. Other factors which have been found to be associated with treatment failure include; viral resistance, low baseline CD4 less than 100cell/µl, a higher baseline viral load, and patients age more than 40years [21-24].

In Tanzania, the most used method to assess the Treatment failure is by Immunological and clinical assessment while virological assessment is seldom done when viral resistance is suspected. Therefore, CD4 count viral load and WHO clinical staging of HIV/AIDS disease may be used respectively. Treatment failure is grouped as Primary virologic failure if there a less than 10 fold drop in viral load after 6-8 weeks of therapy, or when the viral load (VL) is persistently above 10,000 copies/ml. Secondary

virologic failure if there is a 10-fold increase of VL from lowest recorded level. Immunologic failure is defined as a 50% drop in CD4 count from peak value within 6 months, or return to pre-ART baseline CD4 count or lower. Clinical failure results in new disease progression which clinically may present with development of clinical stage 4 opportunistic infections or malignancy occurring 6 months or more after initiation of ART [4].

LITERATURE REVIEW

Emergence of mutant HIV strains that are resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) following a single dose Nevirapine exposure in HIV-1 infected pregnant women has been observed in 33% while there was none in unexposed women[25].

A study done in south Africa showed that increase in Absolute Median CD4 cell count at six and twelve months CD4 cell count,in exposed and unexposed were not statistically significantwith p-valuesof 0.84 and 0.9 respectively. The differences were in respect to the pretreatment CD4+ cell counts[26]. Another study showed that the median increase in CD4+ cell counts was 238 cells/mm^3 overall with an inter-quartile range of 129 to 346 cells/mm^3 [27].A study done in Ivory coast where by women were followed for 36 months revealed that unexposed women had an increase in median CD4+ count of+359 cells/$mm^3$with an IQR of 222 to 491.Women who were exposed had increased median CD4+ counts of +363cells/mm^3 with an IQR of 200 to 464. [28]

An open cohort study done in Zambia where by HIV treatment was provided according to the guidelines showed that there was no significant difference in mean CD4 cell change between those exposed or unexposed to NVP at 6 and 12 months. The mean increase in CD4+ cell count at 6 and 12 months were not statistically significant between exposed and unexposed groups with p-values 0.20 and 0.60 respectively[29]. In a Multi-country study the median CD4+ count among all participants at baseline was 148cells/ml, at 24 wk was 282cells/ml, and at 48 wk was 294cells/ml. The median CD4+ cell count change from baseline to 24 wk was 123cells/ml, and from baseline to 48 wk was 149cells/ml[10]

Anti-retroviral therapy (ART) failure was observed in nearly a third (32.1%) of the Nevirapine exposed women but in only a quarter (25.2%) of the Nevirapine-unexposed women. [10]. In Ivory Coast study nineteen percent (19.8%) of women who initiated HAART met the immunological failure criteria at least once during follow up. The overall probability of immunological failure was 0.08 at 12 months with a 95% confidence interval of 0.12 – 0.15and at 36 months the probability was 0.21 with a 95% confidence interval of 0.16 – 0.27[28]. In another studyimmunological failure was

observed in 11.1% when followed up for 12 months post exposure to PMTCT prophylaxis [27].

Women who recently receivedsdNVP for PMTCT had higher rates of treatment failure when subsequently treated with NVP–based antiretroviral therapy (ART) compared with women treated with NVP-based ART without recent sdNVP exposure. This applied only when NVP-based ART was initiated within 6 months following sdNVP[12]. Women who began ART within 6 months of taking single-dose nevirapine to prevent MTCT were twice as likely to experience ART failure as compared to women who were not exposed to single-dose Nevirapine. Beginning ART 7 to 12 months after single-dose nevirapine was associated with a slight increased risk of ART failure which did not have any statistical difference when compared to unexposed women. Women who began ART more than 12 months after single-dose Nevirapine did not have an increased risk of ART failure compared to unexposed women[10].

In Tanzania, the prevalence of immunological failure was 17.1% [30], and virological failure was 11.8 % [31] both studies did not study the association between ARV prophylaxis for PMTCT and treatment failure

PROBLEM STATEMENT

A single-dose nevirapine (sdNVP) administered around the time of delivery to women was a recommended by World Health Organization (WHO) in 2001and adoped by Tanzania in 2002. In 2007 Tanzania introduced new guidelines on PMTCT which recommendedthe use of more efficacious regimen. [4]. Nucleoside and Non-Nucleoside Reverse Transcriptase Inhibitors based combinations of antiretroviral agents were recommended as first-line regimens for adults and children when ART is needed for the client's health.

By the year 2009, fourty eight percent HIV positive pregnant women received intrapartumsdNVP[6].Single-dose NVP induces viral resistance mutations to non-nucleoside reverse-transcriptase inhibitors (NNRTIs), the rate of which frequency varies from 15% to 67% at 4–6 weeks after delivery in women who receive single-dose NVP alone or after short-course ZDV for prevention of MTCT [11, 33].

In Tanzania, the prevalence of immunological failure was 17.1% [30], and virological failure was 11.8 % [31] both studies did not study the association between ARV prophylaxis for PMTCT and treatment failure.

RATIONALE

In Tanzania the PMTCT program has been in place since 2002 and at various periods sdNVP and the WHO 2006 guidelines have been implemented. There hasn't been,any study that determines the proportion of Immunological response among women who were exposed to PMTCT prophylaxis. It is important to inform the PMTCT and care programs of the safety of the mothers.

Therefore, the aim of this study was to determine the Immunological response to nevirapine based ART in women who were previously exposed to Zidovudine or single dose Nevirapine for PMTCT of HIV whereby levels of the CD4+ counts were the outcomemeasures.

HYPOTHESIS

There is no difference in immunological response to NVP based ART at six and twelve months among women exposed to Zidovudine or single dose Nevirapine Prophylaxis for PMTCT of HIV and those who are not exposed.

OBJECTIVES

Broad objective

To assess the immunological response to antiretroviral treatment of immuno-suppressed women previously exposed to Zidovudine or single dose Nevirapine prophylaxis for Prevention of Mother to Child Transmission of Human Immunodeficiency Virus in Dar es Salaam

Specific objectives

1. To determine and compare proportions of immunological failure and levels of CD4+ cells count at baseline, six and twelve months of the initiation of ART between the women exposed to ZDV or sdNVP for PMTCT prophylaxis and those who were unexposed.
2. To determine and compare proportions of immunological failure and levels of CD4+ cells countsat baseline, six and twelve months of initiation of ART, between women initiated ART less than six months and those who initiated at six months and beyond among women exposed to ZDV/sdNVP for PMTCT prophylaxis.
3. To determine and compare levels of CD4+ cells count and proportions of immunological failure based on the type of ARV exposed to for PMTCT prophylaxis.

METHODOLOGY

Study design

Retrospective cohort study

Study population

Immuno-suppressed women receiving Nevirapine based Antiretroviral Therapy in CTC clinics from four Public Hospitals in – Dar es Salaam

Study sample

All women of reproductive age (15-49) receiving ART for more than one year in CTC.

Study setting

The study was conducted in four CTCs in Public Hospitals in Dar es Salaam, namely Mwananyamala, Temeke, Amana Municipal Hospitals and Muhimbili National Hospital (MNH). Muhimbili National HospitalCTC has a Total of about 7500 clients, whereby females who are on ART are around 3400, and monthly turnover being 1300, whereas most of them are on return visits because MNH recruits an average of 5–10 clients per month. In the three municipal hospitals the number of clients was as follows, Mwananyamala; Total number of clients attending CTC, is 12900, those who are on ART are 7200, monthly turnover is about 4700. Temeke; Total Number of females attending CTC 11,600, on ART age 15-49yrs 3200, turn over in August and September were 3700.Amana; Total number of clients attending CTC, is 12,300, those who are on ART are 5,200, monthly turnover is about 4200.

These hospitals operate the CTC clinics through the support of MDH. Investigations offered include CD4+ cell counts, Viral Load (supposed to be offered when virological failure is suspected but it is done infrequently because of lack of reagents) and other laboratory services like full blood count, liver and renal function test. Laboratory services for CD4+ cell counts are available in all mentioned hospitals while Blood for viral load is withdrawn and transported to the Central Pathology Laboratory (MNH). They are done infrequently because they are highly expensive, though they are scheduled to be taken on six months basis as per guidelines.

HIV/AIDS patients are initiated ART on the National HIV/AIDS treatment guideline 2009 as follows; All patients in WHO stage 4 clinical criteria, regardless of CD4 cell count, Patients in WHO Stage 3 with a CD4 cell count <350/mm^3 as an indicator of their progression to AIDS, All patients with a CD4 count < 200cells/mm^3, regardless of clinical symptoms.The first line regimens are AZT+3TC+NVP, AZT+ 3TC+EFV,d4T+3TC+NVP,d4T+3TC+EFV,TDF+FTC+EFV,TDF+FTC+NVP,TDF+3 TC+EFV,TDF+3TC+NVP.

The patients on ART usually attend at CTC on a monthly basis, for medicine refill and follow up evaluation. The records are kept on the patients files including CTC card number 1 and 2 as well as ART register. The MDH has a Database in the four hospitals where by the patients records are stored. The client Identification Card (CTC1) is a card with a pre-assigned unique client identification number issued at the registration section of the facility during the first visit. The card is for patients on ARV treatment as well as HIV positive clients who are not yet on treatment but are being monitored by the programme. Usually the card stays with the patient.

The client Record Form (CTC2) is a form initiated at the first visit for all HIV positive persons attending the CTC. It is issued by the facility registration unit of the CTC by the attending clinician. The form has a unique ID number, copied from the Patient Identification Card. It is kept in a file and retained in the facility registry or dedicated HIV and AIDS care and treatment cabinet for retrieval at each visit. Important counseling messages stressed is treatment adherence counseling, reporting for adverse reaction nutrition and keeping appointments.

Sample size calculation

$$n = \frac{[Z_\alpha \sqrt{((1+1/m)\bar{p}(1-\bar{p}))} + Z_\beta \sqrt{(p_0(1-p_0)/m) + p_1(1-p_1)}]^2}{(p_0 - p_1)^2}$$

$$\bar{p} = \frac{p_1 + mp_0}{m+1}$$

n is the minimum number of cases required to detect a true relative risk or experimental event rate with power and two-sided type I error probability α (alpha). 5% is the usual choice for α. Power (probability of detecting a real effect) was 90%. β = 1 – power, *m* is the number of unexposed subjects per exposed, $p_0$is the probability of treatment failure in unexposed, p_1 is the probability of treatment failure in exposed, and Z_α *and* Z_β are the standard normal deviate for the probability α and β respectively.

$P_0 = 25.2\%$

$P_1 = 32.1\%$

m = 2

Power = 90%

$Z_\alpha = 1.96$

$Z_\beta = 1.28$

$\dot{p} = 0.2865$

n = 670

n+10% = 737

Therefore 246 in the exposed group and 492 in unexposed group

Research Assisstants

There were two research assistants in every study area, whereby all were Nurses, well trained in counseling. However training of research assistants was done for two days so as to have a common understanding on data collection process. The CTC staffs were preferred as they had the experience to retrieve data from the database, but since the HIV/AIDS carries high index of stigmatization involvement of these counselors made the clients feel more comfortable.

Sampling technique and data collection

During daily registrations, all women on ART for one year or more were screened using CTC2 cards by determining whether they were exposed or not. Those who were exposed were channeled to the research assistants where they were invited to participate in the study after adequate explanation. Those who agreed were asked to consent for the study by signing a consent form then using the questionnaire further interview questions were administered. At the time of screening, that's where using the adherence forms available in the files, were scrutinized for adherence. Those who were picked had good adherence. During the interview by questionnaires, those who reported a history of stopping use of ARVs were not included in the analysis. For every case ,the following 2 unexposed client age 15 to 49 years were recruited for comparison From both groups baseline characteristics were retrieved from their files (age, parity, level of education, CD4+ count, criteria for initiation of ART, WHO clinical staging, Hemoglobin levels, ARVs exposed to and date and type of ART initiated (time elapsed before initiation of ART). The data were collected for two months whereby it was a total of 40 working days and the clients were interviewed until the end of that time.

Data management and Analysis

Data was analysed using SPSS version 16. Standard summary statistics of baseline data was presented, including counts, proportions, medians, and interquartile ranges (IQRs). When appropriate, variables were categorized using standard or clinically relevant cut-points. Comparison of various demographic and medical data among participants of the study population were done using $\chi^2$for categorical variables and Student's t-test was used for normally distributed continuous variables, while Mann-Whitney U tests compared medians when characteristics were not normally distributed.Logistic regression was used to estimate the odds of treatment failure as a function of individual baseline variables.The primary outcome was immunological failure in six months of ART. The new variable was introduced in the SPSS is as to code for immunological failure. Using the two by two tables the proportions of immunological failure were determined.

ETHICAL CONSIDERATION

Ethical clearance was sought from Muhimbili University of Health and Allied Sciences senate, Research and Publication Committee. The study began when the permission was granted by the Director of Muhimbili National Hospital, and Municipal Medical Officers of Kinondoni, Ilala, and Temeke respectively.

Explanations were given, concerning the conduct of the study to participants in terms of all aspects covered in the research, and obtaining a written consent by the study participant before their enrollment. The study participant's personal information was kept confidential and the participants were treated with the utmost respect.

Participants were required to answer questions without feeling embarrassed in case they were unable to answer some of the questions. Assurance to the participants that the decision to participate or not had no effect on their treatment. The participants had a right to refuse to answer some of the questions or withdraw from the study.
Participants who were found in need of treatment and psychological counseling and support were provided with the service as much as it is possible at the level of the facility.

As this was a retrospective study, there were not many ethical issues since both groups were either already exposed or unexposed to the ARV prophylaxis for PMTCT of HIV. Most of the data were retrieved from the files and a few supplementary questions were asked to the clients.

RESULTS

Baseline characteristics

A total of 807 clients were analyzed, among them 288 (35.7%) were exposed to either ZDV/ sdNVP for PMTCT prophylaxis. Exclusion of 68 clients was done because 58 reported a history of stopping the use of ART during the first twelve months, hence poor adherence. There was some missing information from ten clients which necessitated the exclusion (**figure 1**).

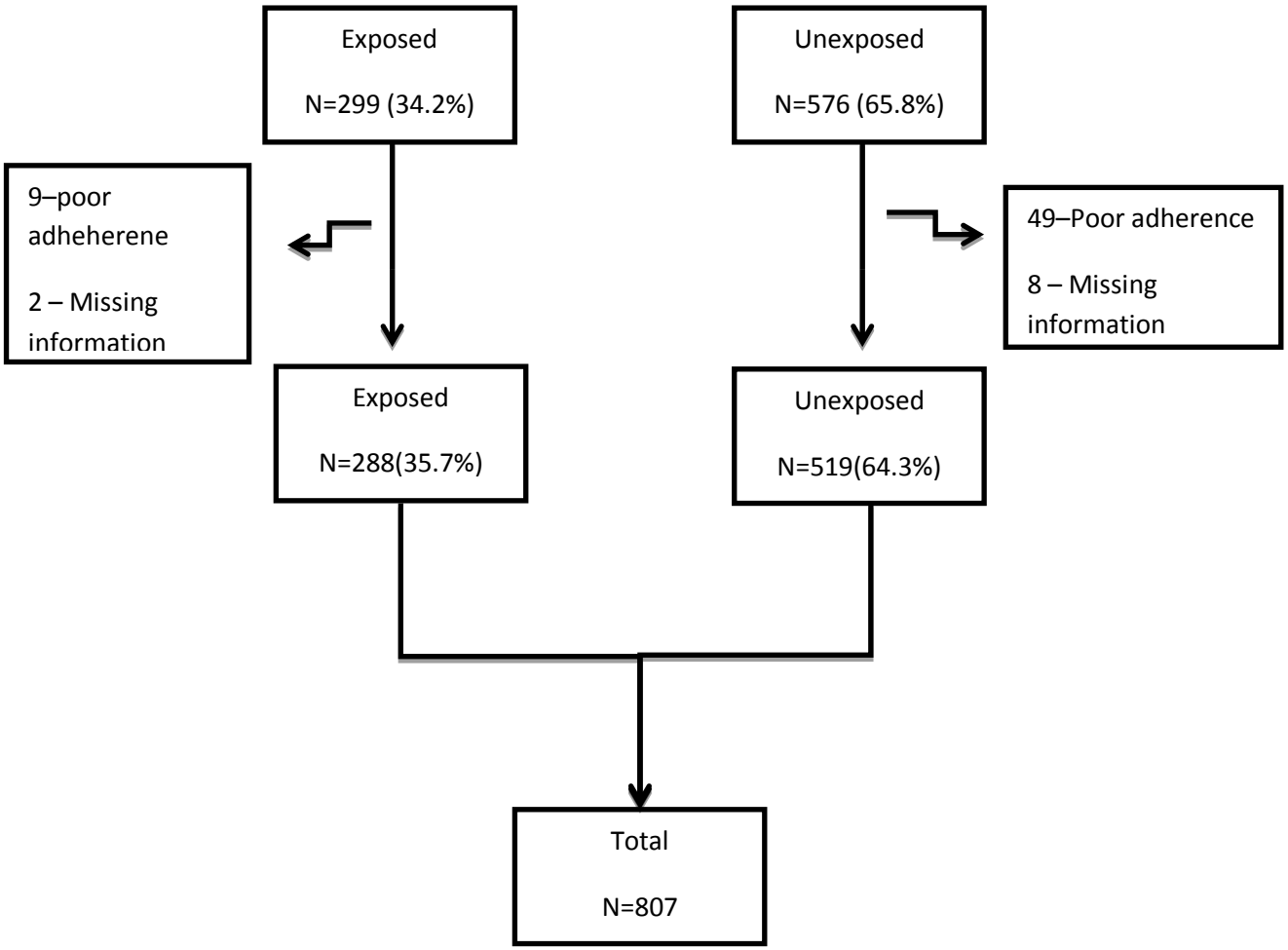

Figure 1: Recruitment of study participants

There was no statistical significant difference in levels of education between the exposed and unexposed.Baseline median CD4+ cell counts in exposed group and unexposed were statistically significant.**(Table 1)**

Table 1: Social demographic data based on exposure status N=807

Characteristics	**Exposed**		**Unexposed**		**Total**	**p-value**
Age	**=n**	**%**	**=n**	**%**		
<29	52	47.3	58	52.7	110	0.25[¥]
30 – 39	185	37.9	303	62.1	488	
≥40	51	24.4	158	75.6	209	
Education level						
No formal education	36	35.0	67	65.0	108	0.37
Primary Education	211	37.0	359	63.0	570	
Secondary and above education	41	30.6	93	69.4	134	
Marital Status						
Not Married	40	33.9	78	66.1	118	0.003
Married/Cohabiting	190	40.1	284	59.9	474	
Divorced/Separated	35	32.1	74	67.9	109	
Widowed	23	21.7	83	78.3	106	
Occupation						
Self employed	124	30.7	280	69.3	404	0.002
Employed	44	34.4	84	65.6	128	
Peasant/House wife	120	43.6	155	56.4	275	
Baseline CD4 count	163*	89–206 **	124*	63-192**		<0.01[Ψ]
Haemoglobin levels						
12g/dl or more	29	33.0	59	67.0	88	0.196
8 – 11.9 g/dl	175	29.5	419	70.5	594	
Less than 8 g/dl	58	46.4	67	53.6	125	
WHO clinical staging						
Stage I& II	28	29.8	66	70.2	94	0.442
Stage III	153	36.3	269	63.7	422	
Stage IV	107	36.8	184	63.2	291	
Initiation of ART after exposure						
Less than six months	106	36.8				
Six Months and after	182	63.2				
Type of ARVs exposed to during PMTCT						
sdNVP only	196	68.0				
ZDV/sdNVP	67	23.3				
ZDV only	25	8.7				

*median CD4+ counts expressed in cells/µl,**inter-quartile range (IQR),[¥]using student's t-test,[Ψ]Mann–WhitneyU test

There was increase in median CD4+ counts of +77 and +164 cell/µl at six and twelve months of ART respectively in Exposed group, while in unexposed group the change was +126 and +196 cells/µl**(Table 2)**

Table 2: Levels of the CD4+ cells counts at baseline, six and twelve months of the initiation of ART between the women exposed to ZDV/sdNVP for PMTCT prophylaxis and those who were unexposed.
N=807

	Exposed n=288		**Unexposed n=519**		**P-Value***
	Median	IQR	Median	IQR	
Baseline	163	89–206	124	63–192	<0.01
At six Months	240	166–346	250	169–349	0.383
At twelve months	327	245–450	320	237–450	0.971

*Mann–Whitney test

Change in median CD4+ cells count at six and twelve months between the two groups were +63 and +170 cells/µl in those who initiated before six months after exposure and those who initiated ART at six months and beyond six months were +79.5 and +160.5 cells/µl respectively**(Table 3A)**.

Table 3A: Levels of the CD4+ cells counts at baseline, six and twelve months of initiation of ART, between women initiated ART before six months and those who initiated at six months and beyond among women exposed to ZDV/sdNVP for PMTCT prophylaxis.

n =288

	<6 months n=106		**≥6months n=182**		**P-Value***
	Median	IQR	Median	IQR	
Baseline	150	85–215	171	93–201	0.067
At six Months	213	142–327	251	180–347	0.271
At twelve months	320	204–500	332	250–421	0.541

*Mann–Whitney U test

Change in median CD4+ cells count at six and twelve months in these two groups were +63 and +182 cells/µl in those who initiated within six months after exposure and those who were unexposed were +126 and +196 cells/µl respectively **(Table 3B)**

Table 3B: Levels of the CD4+ cells counts at baseline, six and twelve months of initiation of ART, between women initiated ART before six months after exposure and those who were unexposed to ZDV/sdNVP for PMTCT prophylaxis.

n=625

	<6months n=106		**Unexposed n=519**		**P-Value***
	Median	IQR	Median	IQR	
Baseline	150	85–215	124	63–192	0.73
At six Months	213	142–327	250	169–349	0.60
At twelve months	332	204–500	320	237–450	0.97

*Mann–Whitney test

Change in median CD4+ cells count at six and twelve months in these two groups were +80 and +161 cells/µl in those who initiated beyond six months after exposure and those who were unexposed were +126 and +196 cells/µl respectively**(Table 3C)**

Table 3C: Levels of the CD4+ cells counts at baseline, six and twelve months of initiation of ART, between women initiated ART at six months and beyond, after exposure and those who were unexposed to ZDV/sdNVP for PMTCT prophylaxis.

n=701

	≥6 months n=182		**Unexposed n=519**		**P-Value**
	Median	IQR	Median	IQR	
Baseline	171	93–201	124	63–192	0.00
At six Months	251	180–347	250	169–349	0.84
At twelve months	332	250-421	320	237–450	0.98

*Mann–Whitney test

The findings were not statistically significant (p-values 0.358, 0.68, 0.926 at baseline, six and twelve months)**(Table 4)**

Table 4: Levels of CD4+ cells count based on the type of ARV exposed to for PMTCT prophylaxis.

n=288

	ZDV,sdNVP and 3TC n=67		**sdNVP n=196**		**ZDV only n=25**		**P-Value***
	Median	IQR	Median	IQR	Median	IQR	
Baseline	166	91–259	169	85–205	129	96–232	0.358
At six Months	265	162–383	234	156–333	248	244–510	0.68
At twelve months	245	245–490	319	245–420	364	244–510	0.926

*Kruskal–Wallis H test

At six months 12.5% of women who were exposed had Immunological failure while only 4.2% of unexposed had immunological failure, which was statistically significant (0.000), and had three times higher risk of developing failure CI (1.86-5.60)**(Table 5)**

Table 5: Proportion of Immunological failure at six months, between women who were exposed to ZDV or sdNVP for PMTCT prophylaxis and those who were unexposed

N=807

Characteristics	**failure =n**	**%**	**No failure**	**%**	**Total**	**RR(95%CI)***	**p-value****
Exposure							
Yes	36	12.5	252	87.5	288	3.1(1.8-5.5)	0.000
No	22	4.2	497	95.8	519		
Age group							
<29	10	9.1	100	90.9	110	2.5(1.0-5.5)	0.043
30 – 39	41	8.4	447	91.6	488		
≥40	7	3.3	202	96.7	209		
Education level							
No formal education	8	7.8	95	92.2	108	0.8(0.3-2.3)	0.828
Primary Education	42	7.4	528	92.6	570		
Secondary and above education	8	6.0	126	94.0	134		
Marital Status							
Not Married	7	5.9	111	94.1	118	0.4(0.1-1.2)	0.085
Married/Cohabiting	32	6.8	442	93.2	474		
Divorced/Separated	14	12.8	95	87.2	109		
Widowed	5	4.7	101	95.3	106		
Occupation							
Self employed	30	7.4	374	92.6	404	1.0(0.6-1.8)	0.124
Employed	4	3.1	124	96.9	128		
Peasant/House wife	24	8.7	251	91.3	275		

*Logistic regression

**χ^2 – test

Immunological failure among those who initiated ART less than six month of exposure to PMTCT prophylaxis occurred in 15.1% as compared to those who initiated six months and beyond 11%. There was no statistical significant difference(p-value 0.357), R.R 1.44, 95%CI (0.7-2.9)

Table 6A:Proportions of immunological failure at six months between women initiated ART before six months and those who initiated at six months or beyond among women exposed to ZDV/sdNVP for PMTCT prophylaxis n=288

Characteristics	Failure n	%	No failure	%	Total	RR(95%CI)*	p-value**
Initiation of ART							
Within six months	16	15.1	90	84.9	106	0.69(0.3-0.5)	0.31
Beyond six months	20	11.0	162	89.0	182		
Type of ART							
ZDV/sdNVP	8	11.9	59	88.1	67	0.45(0.09-2.2)	0.75
sdNVP only	26	13.3	170	86.7	196		
ZDV only	2	8.0	23	92.0	25		
Age group							
<29	6	11.5	46	88.5	52	2.18(0.5-8.8)	0.76
30 – 39	25	13.5	160	86.5	185		
≥40	5	9.8	46	90.2	51		
Education level							
No formal education	5	13.9	31	86.1	36	0.72(0.2-3.4)	0.83
Primary Education	27	12.8	184	87.2	211		
Secondary and above education	4	9.8	37	90.2	41		
Marital Status							
Not Married	1	2.5	39	97.5	40	0.42(0.02-7.4)	0.04
Married/Cohabiting	24	12.6	166	87.4	190		
Divorced/Separated	10	28.6	25	71.4	35		
Widowed	1	4.3	22	95.7	23		
Occupation							
Self employed	18	14.5	106	85.5	124	1.53(0.7-3.4)	0.21
Employed	2	4.5	42	95.5	44		
Peasant/House wife	16	13.3	104	86.7	120		

*Logistic regression

**χ^2 – test

Table 6B:Proportions of immunological failure at six months between women initiated ART before six months and those who were unexposed to ZDV/sdNVP for PMTCT prophylaxis. n= 625

Characteristics	Failure N	%	No failure	%	Total	RR(95%CI)	p-value
Exposure							
Yes*	16	15.1	90	84.9	106	4.2(2.1–8.4)	0.000
No	22	4.2	497	95.8	519		
Age group							
<29	6	7.2	77	92.8	83	4.5(1.1–18.3)	0.021
30 – 39	28	7.6	339	92.4	367		
≥40	3	1.7	172	98.3	175		
Education level							
No formal education	5	6.1	77	93.9	82	1.1(0.3–3.7)	0.988
Primary Education	26	6.0	410	94.0	436		
Secondary and above education	6	5.6	101	94.4	107		
Marital Status							
Not Married	5	5.3	89	94.7	94	0.9(0.3–3.3)	0.123
Married/Cohabiting	17	4.8	340	95.2	357		
Divorced/Separated	10	11.5	77	88.5	87		
Widowed	5	5.7	82	94.3	87		
Occupation							
Self employed	21	6.5	302	93.5	323	0.99(0.5–2.0)	0.356
Employed	3	2.9	101	97.1	104		
Peasant/House wife	13	6.6	185	93.4	198		

*****Initiated ART before six months after exposure to ZDV/sdNP for PMTCT prophylaxis.

Table 6C: Proportions of immunological failure at six months between women initiated ART six months or beyond and those who were unexposed to ZDV/sdNVP for PMTCT prophylaxis.

Characteristics	failure =n	%	No failure	%	Total	RR(95%CI)	p-value
Exposure							
Yes*	20	11.0	162	89	182	2.9(1.5–5.5)	0.01
No	22	4.2	497	95.8	519		
Age group							
<29	6	7.1	79	92.9	85	2.4(0.7–7.5)	0.168
30 – 39	29	6.8	395	93.2	424		
≥40	6	3.1	186	96.9	192		
Education level							
No formal education	6	6.8	82	93.2	88	2(0.6–7.8)	0.427
Primary Education	31	6.3	462	93.7	493		
Secondary and above education	4	3.3	116	96.7	120		
Marital Status							
Not Married	6	5.9	96	94.1	102	1.5(0.4–5.6)	0.621
Married/Cohabiting	23	5.7	378	94.3	401		
Divorced/Separated	8	8.3	88	91.7	96		
Widowed	4	3.9	98	96.1	102		
Occupation							
Self employed	21	5.8	340	94.2	361	0.8(0.4–1.5)	0.25
Employed	3	2.8	105	97.2	108		
Peasant/House wife	17	7.3	215	92.7	232		

*****Initiated ART six months or beyond after exposure to ZDV/sdNP for PMTCT prophylaxis.

DISCUSSION

The levels of CD4+ counts were documented so as to determine the response to the ART between the women who were exposed and unexposed to the PMTCT prophylaxis. Two categories were looked upon those were response, defined as levels of CD4+ counts at six and twelve months after initiation of ART and Immunological failure. The response was termed successfully if there was increase in median cell count of 50cells/µl or more at six months after initiation of ART. The client was termed to have immunological failure if there was no increase in CD4+ or dropping by 50% six months after initiation of ART. Viral load is the best in monitoring the treatment progress; it is unfortunately that we were unable to get the viral load data as they are not done routinely.

Median CD4+ counts of exposed and unexposed were not comparable at baseline; there was statistical difference, as exposed group had higher median CD4+ counts. At six months and twelve months the Median CD4+ counts changed the trend while the unexposed had slightly higher CD4+ counts as compared to exposed, although they were not statistically significant, (p-values 0.383 and 0.971 respectively). The findings could mean that the clients in unexposed group were sicker that the exposed, this might have contributed to insignificant difference at six and twelve months.

The findings are similar to the other study which showed that there was no statistical significant in Immunological response among women who were exposed to PMTCT prophylaxis at six months and twelve months[26]. The study in Ivory Coast where follow up was up to 36 months showed a median increase in CD4+ count was +363 cells/mm^3 and +359 cells/mm^3 in exposed and unexposed women respectively [28]. In Zambia there was no statistically significant increase in mean CD4+ cells counts in six and twelve months of HAART, following exposure to sdNVP[29]. The median CD4+ cells count change did not differ significantly at six and twelve months among exposed and unexposed, in a multi countries studies[10, 34].

The time between exposure and initiation of ART were compared where findings were that, those who initiated ART before six months had poorer immunological response at six and twelve months respectively as compared to those

initiated at six months or beyond. Change in median CD4+ cells count at six and twelve months in these two groups were +63 and +170 cells/µl in those who initiated before six months after exposure and those who initiated ART at six months and beyond were +79.5 and +160.5 cells/µl respectively.The findings are similar to those in a Zambian study where the response of CD4 cell count between women with exposure less than six months and those who started six months and beyond, there was less favorable CD4 cell response at 6 monthswith a median increase of +150 versus +219 cells/µland 12 month an increase in median of +149 versus +215 cells/µl[29]The findings of this study corresponds to other various studies which shows that if the mother waits for at least six months before initiation of ART, is less likely to develop resistance hence poor immunological response and failure, [10, 12]

When comparing median CD4+ cell count according to the type of ARV exposed to, findings were that those who used sdNVP only showed less response to ART at six and Twelve months respectively, as compared to those who used either ZDV/sdNVP or ZDV only. The findings were not statistically significant.The lack of association between sdNVP exposure and immunological response to NVP-based regimens observed in Thailand[10] was also found in a cohort of women followed up in Abidjan, Côte d´Ivoire with a median time from delivery to nevirapine-based antiretroviral therapy of 17 months. No statistical difference in CD4 cell count was observed at 6 and 12 months between single-dose NVP-exposed and non-exposed women (298 cells/ml versus 307 cells/ml). [35]

Seven point two percent of these women had Immunological failure at six months, when taken as per exposure 12.5% of women who were exposed had Immunological failure while only 4.2% of unexposed had immunological failure, which was statistically significant (<0.01), and had three times higher chance of developing failure CI (1.86-5.60), the findings are similar to the study done in Ivory coast which showed that for those women who were exposed to PMTCT prophylaxis, 19.8% of the women who started HAART had immunological failure at least once during follow up. [28] The other study showed that 32.1% of exposed had treatment failure while the

failure in unexposed group was 25.2%[10]. However the treatment failure in this study was based on virological failure rather than immunological.

Immunological failure among those who initiated ART before six month of exposure to PMTCT prophylaxis occurred in 15.1% as compared to those who initiated at six months and beyond 11%. The difference was not statistically significant with p-value 0.357 RR 1.44, CI (0.7-2.9). However when these two groups compared to the group of women who were not exposed to any drug for PMTCT there was strong association between Immunological failure and period between exposure and initiation of ART. Others found that those who initiated ART within six months had twice risk of immunological failure, as opposed by starting beyond that time [10].

Thirteen point three percent of the women who were exposed to the sdNVP only had immunological failure, while those ZDV only had the lowest failure rate of 8%. There was no statistical significant difference.

Strengths of this study are the large sample size, with power of 90%, availability of data that could help in the process and also commitment of research team. Secondly the inclusion of women with good adherence decreased one of the major confounding factors. Taking time as a limiting factor the necessity of doing a retrospective study and hence a possibility of missing those who might have failed treatment or died as they were not in the study area. Another weakness falls in that information which was supposed to be obtained from the client, there could be a recall biashowever; it was a supplementary to the information available in the clients file. Those with known exposures are the one who were included in the study. Being a retrospective study there was inability to control the effect of exposure, effect of difference in baseline CD4+ count, clinical staging and other clinical parameters such as hemoglobin levels.

As noted above there were those who showed Immunological failure and continued with the first line treatment, this could be explained that before the patient is changed to second line thorough scrutiny must be done. This includes proper adherence counseling, counseling on safer sexual behaviors so as to prevent the transmission of resistant viruses. Others include nutrition evaluation and treatment of opportunistic

infections if any. If the patient continues to have persisted lower CD4+ and clinical deterioration then he/she can be subjected to the second line ARVs.

CONCLUSION AND RECOMMENDATION

With these findings we conclude that at baseline, six and twelve months of initiation of ART the statistical significant difference in CD4+ cell count levels was not observed among women exposed to the PMTCT prophylaxis and those who were unexposed. When immunological failure checked as per exposure the findings were statistically significant. Initiation of ART, within six months post exposure, contributed to the poorer CD4+ response significantly as well as immunological failure as compared to those who initiated beyond six months.

This means that as the time passes between exposure to ARVs for PMTCT prophylaxis and initiation of ART, the resistance tends to decrease.

Based on some limitations mentioned above, we recommend that the prospective cohort study to be done, to see the effect of PMTCT prophylaxis to the future use of ART in Tanzania. Implementation of WHO guideline for PMTCT 2012 option B+ may help in reduction of the Immunological failure but if adherence is well maintained.

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APPENDICES

CONSENT FORM FOR PARTICIPATION IN A STUDY

Title:

RESPONSE TO ANTIRETROVIRAL TREATMENT AFTER EXPOSURE TO ZIDOVUDINE OR SINGLE DOSE NEVIRAPINE PROPHYLAXIS FOR PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV IN DAR ES SALAAM

To the Client (A woman attending CTC)

Foreword

I am Dr. MussaMsemo, a postgraduate student at MUHAS conducting a study on response to antiretroviral treatment after exposure to zidovudine or single dose nevirapine prophylaxis for prevention of mother to child transmission of hiv in dares salaam

How to participate

Interview will be conducted between the investigator and the woman who attends the CTC. The evaluation is not compulsory, meaning that any woman is free to accept or refuse to be involved in the study without affecting the activities or treatment conduct.If any problem needing medical attention is diagnosed during examination, appropriate treatment will be given.

Purpose of the Study

The study will help us to determine association between the use of ART for PMTCT and the response when the ARVs are subsequently initiated. The study has the permission from Muhimbili University (MUHAS), the Senate Research and Publication committee.

Risks

The study will not cause any harm to the women participating.

Consent

I have read and understood the explanation of the study. I agree to participate in the study.

For more information or clarification you may contact one of the Doctors mentioned below;

Dr. Mussa K. Msemo Phone number 0717 277456

Dr. Charles Kilewo. Department of Obstetrics and Gynaecology, MUHAS.Dar es Salaam.

Prof. MuhsinAboud, Research chairperson. Phone number 2150302-6

FOMU YA RIDHAA YA KUSHIRIKI KATIKA UTAFITI

Kichwa cha Habari: Utafiti kuhusu mabadiliko ya kinga na virusi kwa wanawake ambao waliwahi kupata dawa za kuzuia maambukizi ya VVU kutoka kwa mama kwenda kwa mtoto na kwasasa wanatumia dawa za kudumaza VVU, Dar es Salaam.

Kwa Mwanamke anayehudhuria clinic ya matibabu na huduma za VVU/UKIMWI,

Utangulizi

Mimi Dk. Mussa Msemo ni mwanafunzi wa shahada ya uzamili Chuo Kikuu cha Afya na Sayansi Shirikishi Muhimbili nafanya Utafiti kuhusu mabadiliko ya kinga na virusi kwa wanawake ambao waliwahi kupata dawa za kuzuia maambukizi ya VVU kutoka kwa mama kwenda kwa mtoto na kwasasa wanatumia dawa za kudumaza VVU, Dar es Salaam.

Taratibu za kushiriki

Wanawake ambao waliwahi kupata dawa za kuzuia maambukizi ya VVU kutoka kwa mama kwenda kwa mtoto na kwasasa wanatumia dawa za kudumaza VVU, Dar es Salaam.Tathmini hii ni ya hiari kabisa, kila mwanamke anayepata huduma kwa ajili ya matatizo yaliyotajwa. Mhusika ana hiari ya kukataa au kukubali, na hii haitaathiri huduma anazopatiwa katika hospitali hizi. Kila mshiriki ataelimishwa endapo atahitaji kuelimishwa,na kama ana tatizo linalohitaji uchunguzi wa kina zaidi au matibabu zaidi atapatiwa kulingana na hospitali au ataelekezwa wapi anaweza kupatiwa huduma anayohitaji.

Dhumuni la Utafiti

Utafiti huu utawezesha kuonyesha uhusiano kati ya matumizi ya dawa za kuzuia maambukizi ya VVU kutoka kwa mama kwenda kwa mtoto na mabadiliko ya kinga na virusi kwa dawa za kudumaza VVU, Dar es Salaam. Utafiti huu umepata kibali kutoka kwa kamati ya jopo la madaktari wa Chuo kikuu cha Tiba cha Muhimbili.

Madhara

Utafiti huu hautasababisha madhara yoyote kiafya kwa washiriki.

Ridhaa ya makubaliano/ kukubali

Nimesoma na kuelewa maelezo kuhusu utafiti huu. Nakubali kushiriki katika utafiti huu.

Kwa ufafanuzi au maelezo zaidi waweza kuwasiliana na mmoja kati ya madaktari wafuatao.

Dk. Mussa K. Msemo simu namba 0717 277 456

Dk. Charles Kilewo, Mhadhiri,Chuo Kikuu cha Afya na Sayansi shirikishi , Muhimbili,Idara ya Uzazi na Magonjwa ya Akinamama.

Prof. Muhsin Aboud ,Mwenyekiti wa kamati ya utafiti. Simunamba 2150302-6

QUESTIONNARES

RESPONSE TO ANTIRETROVIRAL TREATMENT OF IMMUNOSUPPRESED WOMEN PREVIOUSLY EXPOSED TO ZIDOVUDINE OR SINGLE DOSE NEVIRAPINE PROPHYLAXIS FOR PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS IN DAR ES SALAAM

SECTION I: GENERAL INFORMATION/ MaelezoyaJumla				
101	Questionnaire number *NambayaDodoso*	Number:		
102	Name of the hospital *Jina la Hospitali*	Name:		
103	Hospital registration number *Nambayausajilihospitalini*	Number		
SECTION II: SOCIODEMOGRAPHIC CHARACTERISTICS				
Number *Namba*	Questions and filters *Swali*	Response categories *Jibu*		Skip to *Nenda*
201	How old were you on your last birthday? *Unaumriwamiakamingapi*	Age __/__/ *Umri*		
202	What is your religion *Diniyakoipi?*	Christian *Mkristo* Moslem *Muislam*	1 2	

203	Marrital status *HaliyaNdoa*	Single *Mseja* Married *Nimeolewa* Divorced *Nimeachika* Widowed *Mjane* Cohabiting *Kimada/ Naishina bwana* Separated *Tumetengana*	1 2 3 4 5 6 	

	What is the highest educational level you attained? *Kiwango cha juu cha Elimu*	No formal education *Sikusoma* Incomplete primary school *Sikumalizashuleyamsingi* Complete primary school *Nimemalizashuleyamsingi* Incomplete secondary school *Sikumalizashuleyasekondari* Secondary school *Nimemalizashuleyasekondari* College after secondary education *Chuobaada ya shule ya sekondari*	1 2 3 4 5 6	

205	Occupational status Unafanyakazigani	Self employment *Nimejiajiri* Employed *Nimeajiriwa* Peasant *Mkulima* Housewife *Mama waNyumbani*	1 2 3 4	
206	How many pregnancies in total have you had during your life time? *Umeshawahikuwanajumlayamimbangapi?*	Number ____/___		
206	How many deliveries in total have you had in your life time? *Umezaamarangapi*	Number ____/___		
207	How many living children? *IdadiyaWatotowaliohai?*	Number ____/___		
208	What is the age of the last born? *Mtoto wako wa mwisho kumzaa ana umri gani?*	Age ____/___ years		

Question number *Namba*	Questions and filters *Swali*	Response categories *Jibu*	Skip to *Nenda*
301	When were you diagnosed to be HIV positive *Ni lini uligundulika kuwa na VVU?*		
302	After diagnosis did you use any type of medicine *Baadayakugundulikakuwana VVU ulitumiadawayoyote?*	Yes ..... *Ndiyo* No ..... *Hapana*	
303	If yes mention them *Kama ndiyozitaje.*	.....	
304	Have you ever used ARV for PMTCT prophylaxis *Umeshawahikutumiadawazakudumaza VVU kwaajiliyakukingamaambukiziya VVU kutokakwa mama kwendakwamtoto?*	Yes __/__/ *Ndiyo* No __/__/ *Hapana*	Exposed(305) Unexposed (307)
305	Type of prophylaxis used *Ulitumiaainaganiyadawahizo?*	ZDV/sdNVP..... sdNVP only ZDV only	

306	How long did it take between use of prophylaxis and starting ART? *Je ulichukuamudaganikuanzadawabaadayakutumiadawazakudumaza VVU kwaajiliyakukingamaambukiziya VVU kutokakwa mama kwendakwamtoto.*	After.....months of prophylaxis use(delivery) *Miezi..... baadayakutumiadawazakudumaza VVU kwaajiliyakukingamaambukiziya VVU kutokakwa mama kwendakwamtoto.*	
307	When did you start ART? *Ulianzalinikutumiadawazakudumaza VVU kwaajiliyaafyayako?*	____/____/____ *(supported by blue card)*	
307	For how long have you been using ART? *Umeshatumiadawahizokwamudaganisasa?*	.....months Miezi..... *(Supported by blue card)*	
308	What type of ARVs are you using? *Ni dawazipizakudumaza VVU ambazounatumiakwasasa?*	*(Supported by Blue card)*	

309	Did you at any time stopped using ARV? *Tanguumeanzakunawakatiwowote umeshawahikuachakutumiadawah izo?*	Yes..... No.....	go to 310 go to 311
310	For how long did you stop using ARVs *Uliacha kutumia kwa muda gani?*	.....days	
311	What were the criteria for initiation of ART? *Ni kigezoganikilitumikakuanzishada wahizo?*	Blue Card (pts File)	
312	WHO clinical staging		
313	Baseline Hemoglobin levels		
314	CD4+ count	Baseline..... At six months..... At 12 months.....	