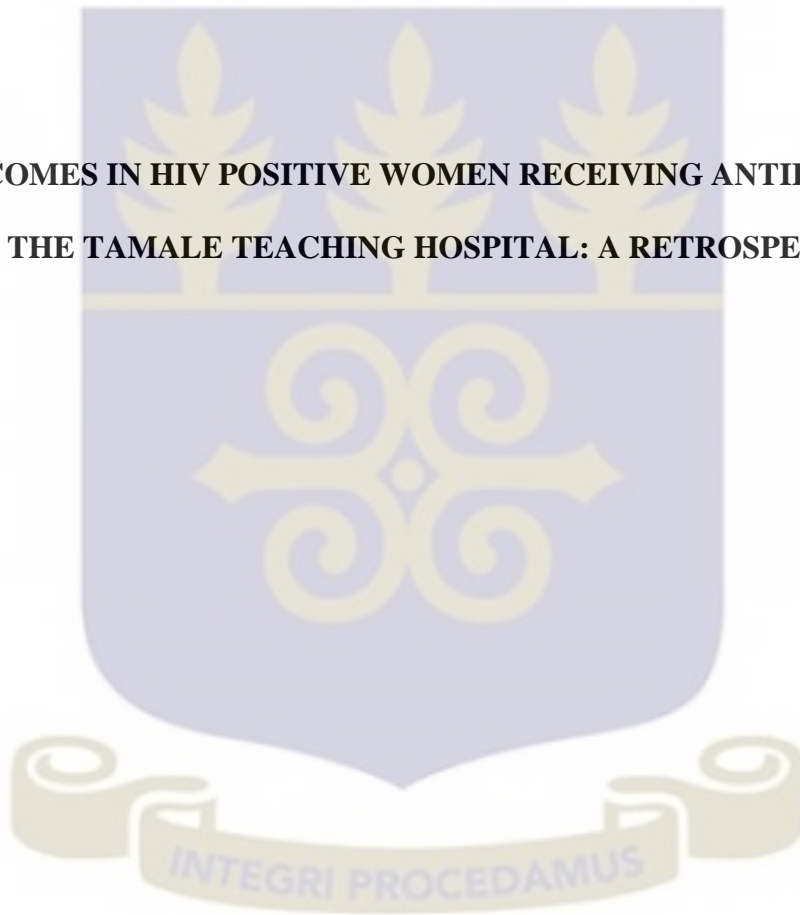


**UNIVERSITY OF GHANA
COLLEGE OF HEALTH SCIENCES
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**BIRTH OUTCOMES IN HIV POSITIVE WOMEN RECEIVING ANTIRETROVIRAL
THERAPY AT THE TAMALE TEACHING HOSPITAL: A RETROSPECTIVE STUDY**



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THERAPY AT THE TAMALE TEACHING HOSPITAL: A RETROSPECTIVE STUDY**

BY

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**THIS DISSERTATION IS SUBMITTED TO THE UNIVERSITY OF GHANA, LEGON
IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF
MASTER OF SCIENCE IN CLINICAL TRIALS DEGREE**

DEPARTMENT OF EPIDEMIOLOGY AND DISEASE CONTROL

JULY 2016

DECLARATION

I, Amandus Ankobil, declare that except for other people's investigations which have been duly acknowledged, this thesis is the result of my own original research, and that this thesis, either in whole or in part has not been presented elsewhere for another degree.

AMANDUS ANKOBIL

(STUDENT)

DATE

DR. ADOLPHINA ADDO-LARTEY

(ACADEMIC SUPERVISOR)

DATE

ABSTRACT

Introduction: There are several conflicting reports on the effect of antiretroviral drugs (ARVs) on birth outcomes in HIV positive women. Studies also suggest that different geographic locations present with varying birth outcomes with respect to specific antiretroviral drugs.

Objective: This sought to examine birth outcomes in HIV positive women who received antiretroviral therapy (ART) at the Tamale Teaching Hospital (TTH) from 2010 to 2015.

Methods: As a result of sparse data on this issue, this Ghanaian retrospective study sought to identify birth outcomes in HIV positive women who received ART in a Ghanaian sentinel clinic between 2010 and 2015. A purposive sampling technique was employed to collect data on birth outcomes from the registry of the ART clinic of the TTH as well as the database of the National AIDS/STI Control Program, Ghana. The Stata software (StataSE 13.0) was used to analyse data. Descriptive data included maternal demographic characteristics and obstetric history as well as ART regimen used. Birth outcomes considered were: newborn's HIV status, low birth weight (<2,500 g), preterm delivery (gestational age <37 weeks) and still births. The Fisher's exact test was used to test for associations between birth outcomes (newborn's HIV seropositivity, low birth weight, preterm delivery and still birth) and ARV regimens as well as maternal risk factors (smoking, alcohol abuse, HIV type, coinfections, education, religion and mode of delivery). The one sample t-test was used to test mean differences of age and birth weight. A p-value below 0.05 was considered statistically significant.

Results: With a mean age of 31.3 ± 5.2 years (CI, 30.21-32.26), the 101 clients' data provided prevalence rates of 4.2%, 18.8%, 7.3% and 5.0% for HIV seropositivity, low birth weight, preterm delivery and still birth respectively. About 85.2% of clients received any one of the following alternative antiretroviral regimens: TDF+3TC+NVP; TDF+FTC+EFV; d4T+3TC+NVP; AZT+3TC+EFV; AZT+3TC+NVP and AZT+3TC. The mean birth weight was 2.9 ± 0.5 (CI, 2.78-2.99). No significant associations were observed between birth outcomes (newborn's HIV seropositivity, low birth weight, preterm delivery and still birth) and respective ARV regimens ($p > 0.05$). Additionally, a-priori confounding maternal risk factors (smoking, alcohol abuse, HIV type, coinfections, education, religion and mode of delivery) assessed in this study were found to have no significant associations with the observed birth outcomes ($p > 0.05$).

Conclusions and recommendations: Birth outcomes were not significantly associated with antiretroviral drug combinations and maternal risk factors. Due to shortages, the sentinel clinic lacked the WHO's recommended ARV regimens for ART. It is critical for key stakeholders to support Ghanaian sentinel clinics obtain preferred antiretroviral regimens (eg. TDF+3TC/FTC+EFV) so as to reduce potential adverse birth outcomes. Also, high priority strategies are required from stakeholders to help reduce mother to child transmission of HIV in order to meet the target of the WHO's Global Plan for eliminating MTCT of HIV while keeping respective mothers alive.

DEDICATION

To Mother Mary and Lovely Wife Theresa



ACKNOWLEDGEMENTS

“Blessed Lord Jesus Christ, I am not worthy that you should unconditionally come under my roof.”

A project such as this does not happen overnight, nor can it be accomplished by flying solo. My supervisor, Dr. Adolphina Addo-Lartey never ceases to amaze me with her scholarly advice with a generous spirit and enchanting expertise at the ready. I am truly thankful for her stellar inputs from start to end. Despite the Ghana Health Service granting ethical approval for executing this work, this study would not reach this far but for the assistance of the Ghana National AIDS/STI Control Programme [NACP] who provided me with limited access to datasets appropriate for this study. Worthy of mention are Dr. Stephen Ayisi Addo, the NACP's Programme Coordinator for approving the data sharing agreement certificate; Mr. Gyasi, the NACP's Administrator for facilitating the process faster than I could imagine and Mr. Ekow Wiah for sorting out the datasets apt for this study.

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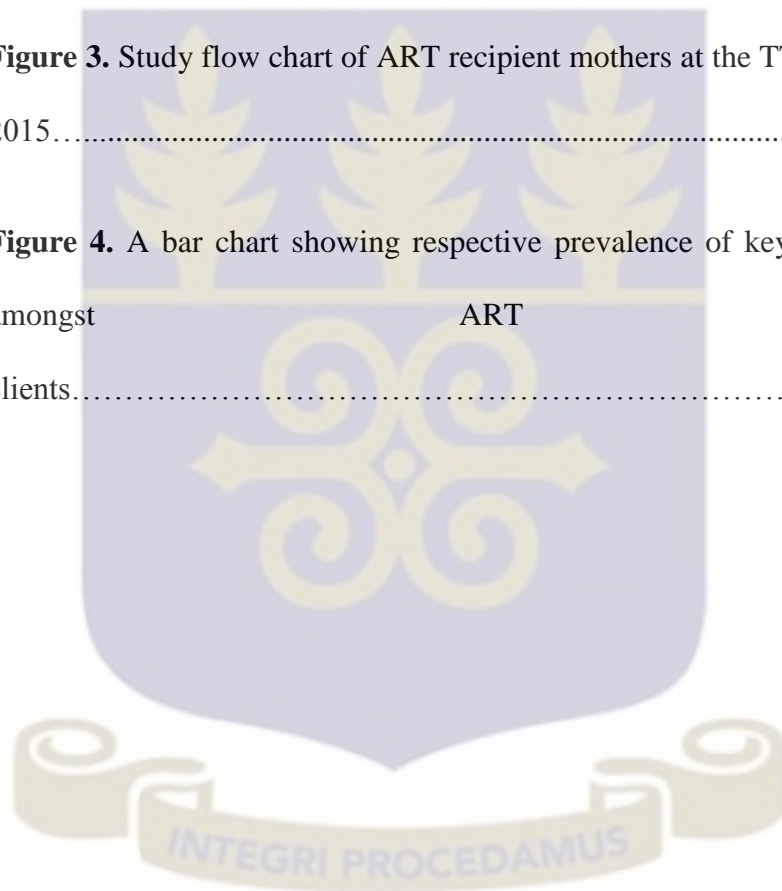
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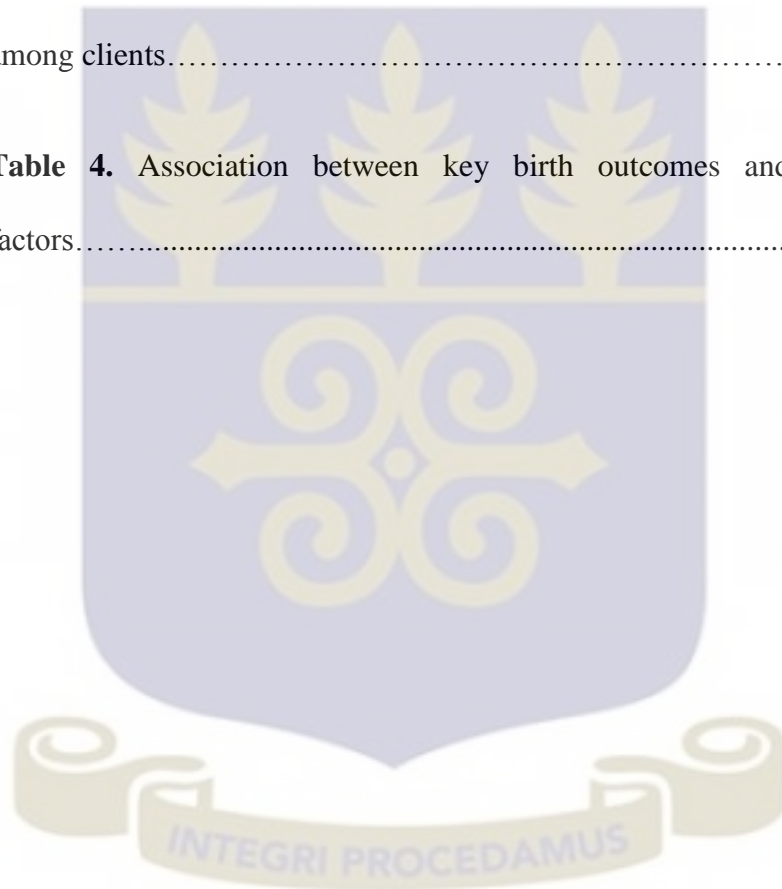
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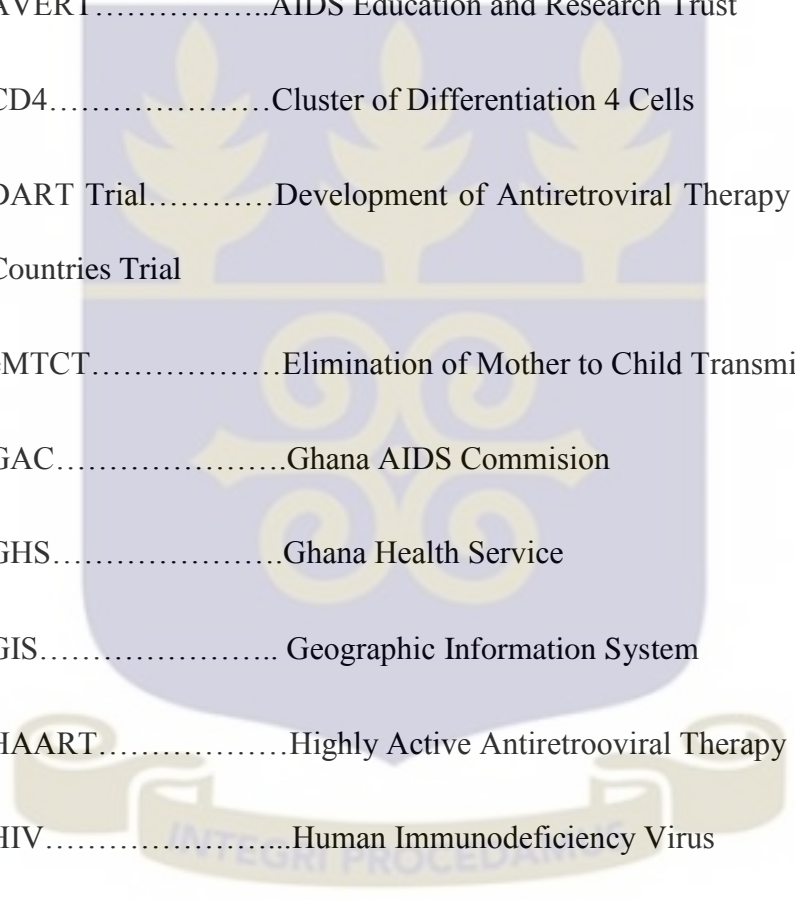


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LIST OF ABBREVIATIONS / ACRONYMS



AIDS.....	Acquired Immunodeficiency Syndrome
ART.....	Antiretroviral Therapy
ARVs.....	Antiretroviral drugs
AVERT.....	AIDS Education and Research Trust
CD4.....	Cluster of Differentiation 4 Cells
DART Trial.....	Development of Antiretroviral Therapy for Developing Countries Trial
eMTCT.....	Elimination of Mother to Child Transmissions
GAC.....	Ghana AIDS Commision
GHS.....	Ghana Health Service
GIS.....	Geographic Information System
HAART.....	Highly Active Antiretrooviral Therapy
HIV.....	Human Immunodeficiency Virus
II.....	Integrase Inhibitors
MTCT.....	Mother to Child Transmission of HIV
NACP.....	National AIDS/STI Control Programme, Ghana
PMTCT.....	Prevention of Mother to Child Transmission

MACDP.....The Metropolitan Atlanta Congenital Defects Programme

MTCT.....Mother to Child Transmission of HIV

NIAID.....National Institutes of Allergy and Infectious Diseases

NNRTIs.....Non-Nucleotide Reverse Transcriptase Inhibitors

NRTIs.....Nucleotide Reverse Transcriptase Inhibitors

PI.....Protease Inhibitors

PMTCT.....Prevention of Mother to Child Transmission

STI.....Sexually Transmitted Infections

TTH.....Tamale Teaching Hospital

UNAIDS.....Joint United Nations Programme on HIV/AIDS

UNICEF.....United Nations International Childrens' Fund

WHO.....World Health Organisation



CHAPTER ONE

INTRODUCTION

Background

Globally, an estimated 36.7 million [34.0-39.8 million] people were living with Human Immunodeficiency Virus (HIV) at the end of 2015 (UNAIDS, 2016). Over 90% of infections in children result from mother-to-child transmission (MTCT) while 1,600 children are infected by the HIV through MTCT each day (Alemu, Yalew, Fantahun, & Ashu, 2015). Mortality from AIDS also remains high in Africa due to extensive unmet treatment needs and Ghana, despite impressive efforts in the fight against HIV/AIDS, still has a long way to go (Addo, Yawson, Addo, Dornoo, & Seneadza, 2014). Recent advances in the knowledge of human immunodeficiency virus (HIV) biology, pathogenesis and therapy, and their dramatic positive consequences on HIV-related morbidity and mortality, are quite unique in the history of medicine (Palmisano & Vella, 2011). More importantly, antiretroviral (ARV) therapy is potent, convenient and usually well tolerated (Palmisano & Vella, 2011).

In fact, one of the major successes in the management of HIV- positive patients has been the PMTCT of HIV (Taylor et al., 2012). The massive global expansion of access to HIV treatment has transformed not only the HIV epidemic but the entire public health landscape, demonstrating that the right to health can be realized even in the most trying of circumstances (UNAIDS, 2013). Maximum benefit for maternal health and fetal protection is obtained through the use of combination antiretroviral therapy (ART), including highly active antiretroviral therapy (HAART) (Tuomala et al., 2005) and hence

keeping mothers alive and healthy is instrumental for child survival (UNAIDS, 2013).

The WHO, in 2013, pointed out that an AIDS-free generation starts in the first decade of life. This resulted in leadership supporting 19 of the 22 focus countries in their efforts to attain the goals of the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive while also adopting policies to initiate antiretroviral therapy (ART) among all HIV-positive pregnant and breastfeeding women. These efforts underline the UNICEF commitment to place the health of the mother first in curbing the epidemic in the first decade of a child's life (UNICEF, 2013). Since the establishment of this agenda, and in comparison to the 22 priority countries on this Global Plan, Ghana has made the best efforts to reduce mother-to-child-transmission (MTCT) of HIV (UNICEF, 2013). Moreover, Ghana like many high-burden countries has made significant advances towards increasing availability of HIV-testing during pregnancy and provision of ART to prevent mother-to-child transmission (PMTCT) of HIV (GHS, 2014; Kendall & Danel, 2014).

Despite such advances, some areas such as the Greater Accra and Eastern Regions of Ghana still record high prevalence in HIV infections while other areas particularly in Northern Ghana record very low prevalence rates (Ghana AIDS Commission [GAC], 2013). With a national prevalence of 1.37%, the respective prevalence of HIV in the Greater Accra and Northern Regions of Ghana are 3.2% and 0.6% (National AIDS/STI Control Programme [NACP], 2016). In addition, the national HIV prevalence rate in Ghana fell to 1.6% in 2014 from 1.9% in 2013, the first recording below 2% in two decades (GAC,

2013) while HIV prevalence amongst pregnant women attending antenatal clinic for 2013 is 1.9% a drop from 2.1% in 2012. In the Central Region of Ghana however, the Cape Coast Teaching Hospital (CCTH), the main regional referral centre, recorded 209 cases in 2014 as opposed to 161 cases in 2013, an alarming 30% rise (NACP, 2014). Neonatal infections are also on the increase at this facility where 5, 112 HIV patients visit the hospital for clinical follow-ups while 774 HIV positive individuals including 49 children were receiving ART (NACP, 2014).

Contrastingly, in Ghana as well as several sub-Saharan African countries, insufficient integration of HIV and Maternal and Child Health (MCH) services persists and opportunities to improve women's health by addressing comorbidity factors are missed (Kendall & Danel, 2014). Also, rates of uptake, linkage between maternal and child health (MCH) and HIV care, retention and ART adherence are suboptimal while very few studies of adverse birth outcomes have been reported in HIV positive pregnant women receiving ART (Bagkeris et al., 2015).

Nowadays, antiretroviral drugs (ARVs) are helping people have a better/normal life and this has resulted in tremendous success over the years (since 1994) as far as the prevention-of-mother-to-child-transmission (PMTCT) is concerned (UNAIDS, 2013). This has also served a good cause for the global population as more HIV-positive pregnant women yearn to have babies (Myer et al., 2010; Taylor et al., 2013; Poda et al., 2016). It is unfortunate however, that antiretroviral drugs (ARVs) especially the protease inhibitors (PI) have been shown to be associated with adverse birth outcomes (including HIV seropositivity, low birth weight [LBW] and preterm deliveries [PTD]) with

these outcomes differing from setting to setting (Alemu, Yalew, Fantahun, et al., 2015). This erodes the benefits of ARVs and targets set out for the PMTCT. What is more, these reports are mixed and leaves the scientific community in a state of uncertainty especially in sub-Saharan Africa (Aniji, Towobola, Hoque, Mashamba, & Monokoane, 2013). Also, adverse birth outcomes resulting from ART in Ghana are sparse in scientific literature. Thus, mixed global trends of birth outcomes coupled with a lack of scientific evidence pertaining to the Ghanaian situation could derail the targets set by the UNAIDS to end the AIDS epidemic by 2030. Moreover, understanding the factors that affect adverse birth outcomes is crucial to public health policy makers in Ghana (Ibrahim & Keefe, 2014) if they are to effectively produce a healthy Ghanaian population. Thus, considering the fact that Ghana provides the best outlook for elimination of mother-to-child-transmissions (eMTCT) amongst the 22 priority countries on the Global Plan, a poor understanding of ART-related adverse birth outcomes would ultimately lead the country back from where she emerged a few decades ago.

Problem statement

Several studies reveal a possible role of ART on adverse birth outcomes despite other studies not concurring (Cotter, Garcia, Duthely, Luke, & O'Sullivan, 2006). Amongst such studies are key studies from Brazil and North America which show no association between maternal ART use and pregnancy outcomes (Aniji et al., 2013). For instance, data on 1,973 and 1,767 in utero ART exposed and non-exposed newborns of mixed race revealed that 1.4% of

newborns unexposed to ART had a congenital abnormality (including LBW and PTD) compared to 1.6% of those exposed (Patel, Thorne, Fiore, & Newell, 2006). Another cohort study conducted between 1997 and 2005 on 206 HAART (with 176 mothers on PI) exposed and 206 unexposed newborns demonstrated no significant differences in PTB and LBW between groups: with 10.6% PTB in exposed newborns compared to 7.8% PTB in the unexposed group as well as 9.9% LBW in exposed versus 5.3% LBW in controls (Carcella et al., 2009).

Other studies contradict these findings. First, a systematic review of 1,124 papers from 2003-2013 using 32 methodologically fit studies frequently observed LBW and PTB from ART in developing countries (Alemu et al., 2015). Second, a Ukrainian study between using data on 7,435 HIV-positive mothers on ART between 2000 and 2012 showed 9% of live births for PTB and LBW respectively (Bagkeris et al., 2015). In Africa, only a few reports are available on the impact of ART on birth outcomes (Nlend, Esther, Zeudja, Moyo, & Motaze, 2014). A classic example involves an Ethiopian study among 416 newborns exposed to HAART from 2009 to 2012 reported the prevalence of LBW and PTB as 21.4% and 16.6% respectively (Kebede, Andargie, & Gebeyehu, 2013). Other studies from Nigeria and Cote d'Ivoire revealed an association between ART and LBW as well as other maternal complications (Aniji et al., 2013). In the case of Ghana, limited data exists as far as the specific role of ART on birth outcomes is concerned. Despite been the best ranked amongst 22 priority countries on the Global Plan, the Ghana Health Service's 2014 Handbook for the PMTCT does not include as a priority strategy, directives to record adverse birth outcomes from ART (GHS, 2014). As though to climax the problem, recent systematic reviews by the WHO revealed huge

evidence gaps in the potential increased risk of adverse events associated with the long-term use of ARV drugs during pregnancy and in breastfeeding mothers (WHO, 2013).

Justification

Low birth weight (LBW) and preterm deliveries (PTD) are key indicators of an infant's health status (United States Environmental Protection Agency, 2013). Therefore the health of any nation depends on a future generation that presents with normal birth outcomes and thus a positive step towards achieving the Millennium Development Goal-4 (MDG-4) (Ibrahim & Keefe, 2014). Concerns about the efficiency as well as uncertainties about birth outcomes from antiretroviral drug usage among HIV-positive women require an evaluation of the effects of ARVs on birth outcomes. This is properly monitored by the UK Collaborative HIV Cohort Study which collects data from UK's largest HIV treatment centres (Jose et al., 2014). More so, it is crucial for public health experts to ascertain key associations between outcomes such as newborn seropositivity, low birth weight (LBW), still birth, preterm delivery (PTD) and comorbidities such as maternal adherence to ART, duration of ART, nutrition, genetics and smoking (Jose et al., 2014; Alemu et al., 2015). Such data are lacking especially in developing countries like Ghana.

The conflicting reports and variations between countries on the effect of ART on birth outcomes call for country specific studies and public health guidelines to determine advances made upon the introduction of ARVs to prevent MTCT of HIV (Alemu et al., 2015). As a result, this study seeks to

identify adverse birth outcomes in HIV positive women who received ART in the Tamale Teaching Hospital (TTH) of Ghana from 2010 to 2015. Key associations between these outcomes and ARVs will also be derived from the study. A thorough understanding of adverse birth outcomes is crucial to public health policy makers in Ghana while suitable country specific ARV combinations for eMTCT of HIV is critical for Ghana to develop high priority strategies for PMTCT of HIV.

Conceptual framework

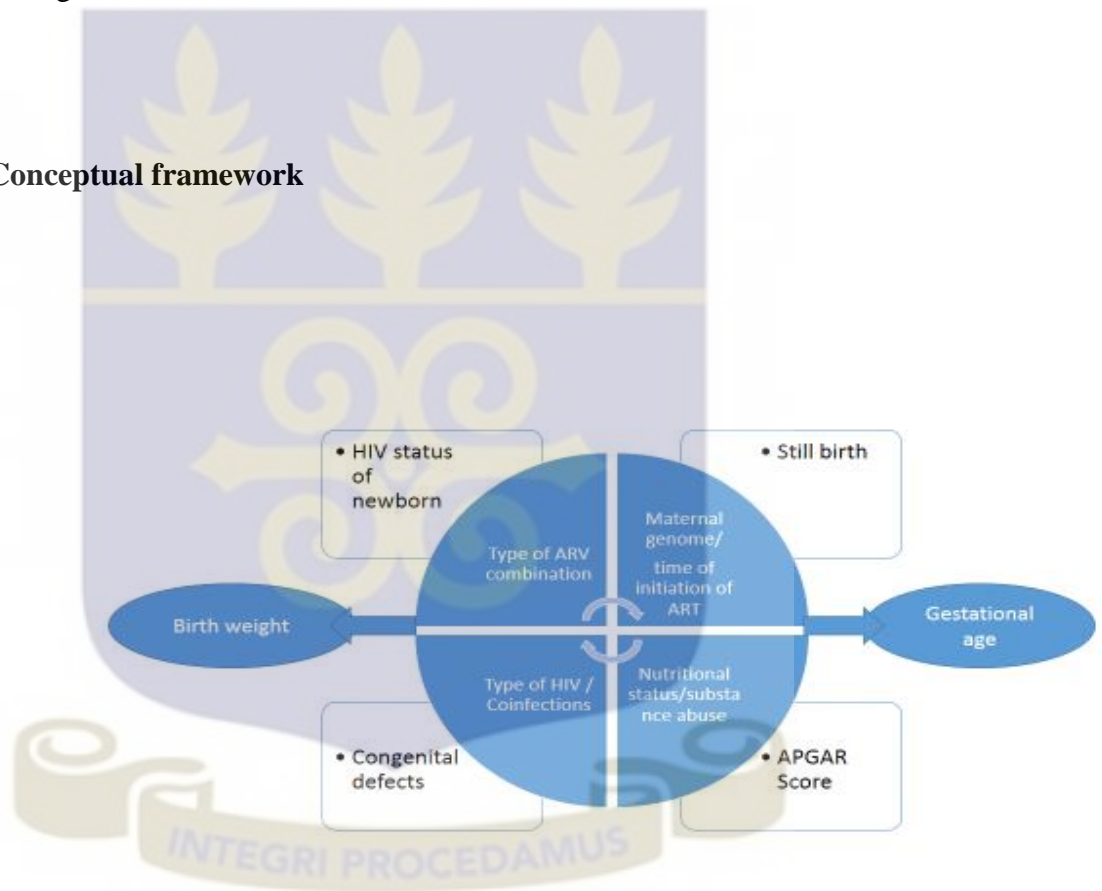


Figure 1. A conceptual framework illustrating interactive maternal factors and resultant birth outcomes from HIV positive women receiving ART (Adapted from Alemu et al., 2015)

The model describes expected ART-related birth outcomes among HIV-infected women as well as the covariates associated with adverse birth outcomes in the aforementioned group (Taylor et al., 2012). The curved arrows

demonstrate a possible association between maternal comorbidity factors with ART and a resultant impact on adverse birth outcomes (Alemu et al., 2015). It is also clear the role of confounding and or interfering comorbidity factors such as maternal genome, coinfections such as tuberculosis, type of HIV, nutritional status, substance abuse, etc (Kebede et al., 2013; Riva, Malik, Burnie, Endicott, & Busse, 2012; Taylor et al., 2012). In the model, ART is the primary independent factor influencing the outcome variables herein called birth outcomes. The expected birth outcomes include newborn's HIV status, low birth weight (LBW), preterm delivery (PTD), still birth, APGAR score and congenital defects (Tuomala et al., 2005; WHO, 2013). Despite literature pointing to negative seropositivity of newborns from ART receiving mothers, there have been recently reported instances of a 1-2% prevalence of HIV in newborns from ART receiving mothers and this calls for in-depth research focus (WHO, 2013).

Research questions

As far as the association between birth outcomes and ART is concerned, pertinent questions that will keep scientists very busy for at least one more decade include the following (Palmisano & Vella, 2011):

- What is the impact of ARVs on birth outcomes?
- How do maternal factors exacerbate these outcomes?
- When is the best time to start antiretroviral therapy during pregnancy?
- Which is the best ARV combination for ART?

Main objective

This study seeks to examine birth outcomes in HIV positive women who received antiretroviral therapy (ART) at the Tamale Teaching Hospital (TTH) from 2010 to 2015.

Specific objectives

- To determine the prevalence of HIV among newborns exposed to HIV positive mothers on ART.
- To determine the prevalence of low birth weight (LBW) among newborns born to ART recipient HIV-positive mothers.
- To determine the prevalence of stillbirths in ART recipient HIV-positive mothers.
- To assess the prevalence of preterm deliveries arising from HIV-positive mothers on ART.
- To ascertain the association between birth outcomes and different antiretroviral drug (ARV) combinations.

CHAPTER 2

LITERATURE REVIEW

2.1 The Human Immunodeficiency Virus (HIV)

The HIV was first identified in 1981 but it was not until 1984 when evidence became available that the virus was associated with the Acquired Immunodeficiency Syndrome (AIDS). HIV is mainly transmitted via the parenteral or sexual route and is characterized by a depletion in CD4 cells (Palmisano & Vella, 2011). The earliest form of the virus as identified in 1981 was classified as HIV-1 while another form, the HIV-2 was discovered in West Africa in 1986. HIV-1 has a global distribution as opposed to HIV-2 which is prevalent in the West African sub-region. HIV-1 and HIV-2 share many similarities including their basic gene arrangement, modes of transmission, intracellular replication pathways and clinical consequences: both result in AIDS. However, HIV-2 is characterised by lower transmissibility and reduced likelihood of progression to AIDS. The underlying mechanistic differences between these two infections illuminate broader issues of retroviral pathogenesis, which remain incompletely understood (Nyamweya, 2013).

2.2 HIV in Ghana

The first confirmation of HIV in Ghana was done at the Noguchi Memorial Medical Research Institute in 1986 (Addo et al., 2014). Data on the prevalence and incidence of HIV is usually monitored by the National AIDS/STI Control Programme using findings of the yearly HIV Sentinel Survey

Report [HSS, 2014]. This cross sectional survey largely utilizes data from HIV infected pregnant women across the forty sentinel sites across Ghana. The findings of this survey have been very useful as a good proxy indicator of the prevalence or spread of HIV among the Ghanaian people (HSS, 2014). As of 2014, an estimated 250,000 people are living with the virus while the prevalence rate among adults aged 15-49 years is 1.4% (GAC, 2016). By the estimates, another 21, 000 children aged 0-14 years are living with HIV in Ghana. HIV prevalence in Ghana is highest in the Greater Accra Region at 3.2% and lowest in the Northern Region at 0.8%. Mother-to-child transmission accounts for 15% of cases while heterosexual modes of transmission accounts for about 80% of HIV cases in Ghana (UNAIDS, 2014).

As expected over 95% of HIV cases in Ghana are due to HIV-1 (Addo et al., 2014; Mensah, 2013). HIV prevalence amongst pregnant women attending antenatal clinic for 2013 is 1.9% a drop from 2.1% in 2012. It is the first recording below 2% in two decades. The prevalence of HIV is also higher in urban areas of Ghana (GAC, 2014). In fact it is worthy of note that as at 2014, the Eastern Region of Ghana was noted for recording the highest HIV prevalence in Ghana since the epidemic was identified in 1986, recorded the highest prevalence of HIV at 3.7% but has now declined to 3.1% as findings from the 2015 HIV Sentinel Survey Report show. Interestingly, the 2015 HIV Sentinel Survey Report indicates that the Greater Accra Region now tops in prevalence at 3.2%, a rise from 3.1% in 2014, an indication of the drastic decline in prevalence recorded by the Eastern Region.

2.3 Antiretroviral drugs (ARVs) for HIV treatment

The most significant advance in the medical management of HIV-1 infection has been the treatment of patients with antiviral drugs, which can suppress HIV-1 replication to undetectable levels (AIDS Education and Research Trust [AVERT], 2015). The discovery of HIV-1 as the causative agent of AIDS together with an ever-increasing understanding of the virus replication cycle have been instrumental in this effort by providing researchers with the knowledge and tools required to prosecute drug discovery efforts focused on targeted inhibition with specific pharmacological agents (Arts & Hazuda, 2012).

There are currently more than 20 approved antiretroviral drugs in the US and Europe (including combined formulations) and many more in the expanded access programmes and clinical trials. Most antiretroviral drugs have at least three names (AVERT, 2015). Sometimes a drug is referred to by its research or chemical name, such as AZT for zidovudine. The second name is the generic name for all drugs with the same chemical structure; for example AZT is also known as zidovudine. The third name is the brand name given by the pharmaceutical company; one of the brand names for zidovudine is Retrovir. Lastly, an abbreviation of the common name might sometimes also be used, such as ZDV, which is the fourth name given to zidovudine.

These drugs are distributed into five distinct classes based on their molecular mechanism and resistance profiles: nucleoside-analog reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs); integrase inhibitors (IIs), protease inhibitors (PIs); fusion inhibitors

(FIs), and chemokine receptor/coreceptor antagonists. The table below summarizes the various classes of ARVs with respective examples (AVERT, 2015).



Table 1. Classes of ARVs with respective examples, abbreviations and dates of approval

Class	Drugs	Abbreviation	Date of FDA Approval
nucleoside-analog reverse transcriptase inhibitors (NRTIs)	lamivudine	3TC	17-Nov-95
	abacavir	ABC	17-Dec-98
	zidovudine	AZT or ZDV	19-Mar-87
	stavudine	d4T	24-Jun-94
	didanosine	ddI	31-Oct-00
	emtricitabine	FTC	02-Jul-03
	tenofovir	TDF	26-Oct-01
non-nucleoside reverse transcriptase inhibitors (NNRTIs)	delavirdine	DLV	04-Apr-97
	efavirenz	EFV	17-Sep-98
	etravirine	ETR	18-Jan-08
	nevirapine	NVP	21-Jun-96
	rilpivirine	RPV	20-May-11
protease inhibitors (PIs)	Amprenavir	APV	15-Apr-99
	Fosamprenavir	FOS-APV	20-Oct-03
	Atazanavir	ATV	20-Jun-03
	Darunavir	DRV	23-Jun-06
	Indinavir	IDV	13-Mar-96
	Lopinavir+ritonavir	LPV/RTV	15-Sep-00
	Nelfinavir	NFV	14-Mar-97
	Ritonavir	RTV	01-Mar-96
	saquinavir	SQV	06-Dec-95
	Tipranavir	TPV	22-Jun-05
Fusion inhibitors (FIs)	enfuvirtide	T-20	13-Mar-03
	maraviroc	MVC	18-Sep-07
Integrase inhibitors (IIs)	raltegravir	RAL	12-Oct-07

2.4 Highly Active Antiretroviral Therapy (HAART)

HAART is a customized combination of different classes of medications that a physician prescribes based on such factors as the patient's viral load, the particular strain of the virus, the CD4⁺ cell count, and other considerations (e.g., disease symptoms). These multi-class combination products combine HIV drugs from two or more classes, or types, into a single product. To prevent strains of HIV from becoming resistant to a type of antiretroviral drug, healthcare providers recommend that people infected with HIV take a combination of antiretroviral drugs in an approach called highly active antiretroviral therapy (HAART). Because HAART cannot rid the body of HIV, it must be taken every day for life (National Institute of Health [NIH], 2006). HAART can control viral load, delaying or preventing the onset of symptoms or progression to AIDS, thereby prolonging survival in people infected with HIV.

HAART has been in use since 1996 and has changed what was once a fatal diagnosis into a chronically managed disease. Since the introduction of HAART in 1996 and 1997, there has been a significant decline in mortality and morbidity associated with HIV (Mocroft & Lundgren, 2004). Maximum benefit for maternal health and fetal protection is obtained through the use of combination ART, including highly active antiretroviral therapy (HAART) (Tuomala et al., 2005). Developed by NIAID (National Institutes of Allergy and Infectious Diseases)-supported researchers, HAART combines drugs from at least two different classes. In recent years, drug companies have worked together to combine these complex regimens into simpler formulas, termed

fixed-dose combinations. Some of these drug class combinations with their brand names in parenthesis include: lamivudine + zidovudine (combivir), emtricitabine+tenofovir+efavirenz and abacavir+lamivudine+zidovudine (trizivir).

2.5 ART in Ghana

The largest clinical trial in Africa, the Development of Antiretroviral Therapy in Africa (DART) trial, was conducted at various centres in Uganda and Zimbabwe between January 15, 2003 and October 24, 2004 to investigate whether delivery of ART with or without routine monitoring of CD4-cell counts for efficacy, and haematology and biochemistry for safety, led to similar outcomes in HIV- infected patients receiving ART who had already fulfilled clinical and CD4-count criteria to start ART (DART, 2010). As a consequence, ART was piloted in Ghana in 2003 (Ohene & Forson, 2009).

The programme started at two hospitals in the Eastern Region where, at the time, the highest HIV prevalence was recorded. Another programme aimed at prevention of mother-to-child transmission (PMTCT) of HIV using a single dose Nevirapine was initiated. Both programmes were gradually scaled up to cover the entire country by 2010 (Brandful, 2015). As at the end of 2012, 73,339 including 3,461 children were on treatment in Ghana. The PMTCT strategy has also changed from an era of single-dose Nevirapine through dual therapy with Zidovudine and Lamivudine to HAART for all pregnant women irrespective of CD4 counts (GHS, 2014). This has led to a 76% decline in the number of new infections in children over three years (2009 to 2012). In Ghana, antiretroviral

therapy used to be provided through a government-sponsored program. Patients would then pay a subsidized monthly fee of 5 Ghana cedis for counselling, doctor's visit and antiretroviral medication (Howley et al., 2010). Today, the Ghanaian Government has found immense funding support from the Global Fund for supplying free antiretroviral drugs to HIV clients.

Studies in Africa recommend important follow-up studies of the ART programme including the examination of determinants of ART adherence and to test whether there are significant differences between centres or between the public and private health sectors (Addo-Atuah et al., 2012). Regular attendance at follow-up as well as family support have been shown to be vital factors for 100% lifetime medication adherence. Moreover, studies have recommended that Ghana needs to place strong emphasis on effective counseling sessions on adherence for patients on antiretroviral therapy if the nation is to realize the purpose and benefits of antiretroviral therapy programmes (Obirikorang, Selleh, Abledu, & Fofie, 2013).

2.6 Global update on ART and WHO guidelines

The massive global expansion of access to HIV treatment has transformed not only the HIV epidemic but the entire public health landscape, demonstrating that the right to health can be realized even in the most trying of circumstances (UNAIDS, 2013). While the world has committed to ending the AIDS epidemic by 2030, the strategies that would lead to this bold target within the Sustainable Development Goals was a central question for discussion at the United Nations General Assembly High-Level Meeting on Ending AIDS, held

in June, 2016. The good outlook is the extraordinary accomplishments of the last 15 years, and this outlook inspires global confidence that this target can be achieved. Today, after the Global Plan's target of 2015, the UNAIDS recommends a Fast-Track approach comprising two key strategies. First, substantially increasing and front-loading investment over the next five years to accelerate scale-up and second, establishing the momentum required to overcome within 15 years one of the greatest public health challenges in this generation.

Indeed, the latest UNAIDS data, covering 160 countries, demonstrate both the enormous gains already made and what can be achieved in the coming years through this Fast-Track approach. In just the last two years, the number of people living with HIV on antiretroviral therapy has increased by about a third, reaching 17.0 million people - 2 million more than the 15 million by 2015 target set by the United Nations General Assembly in 2011. Since the first global treatment target was set in 2003, annual AIDS-related deaths have decreased by 43%. In the world's most affected region, eastern and southern Africa, the number of people on treatment has more than doubled since 2010, reaching nearly 10.3 million people. More so, AIDS - related deaths in the region have decreased by 36% since 2010.

However, huge challenges lie ahead. In 2015 there were 2.1 million [1.8 million-2.4 million] new HIV infections worldwide, adding up to a total of 36.7 million [34.0 million-39.8 million] people living with HIV. Scale-up of antiretroviral therapy is on a Fast-Track trajectory that has surpassed expectations. Global coverage of antiretroviral therapy reached 46% [43-50%] at the end of 2015. Gains were greatest in the world's most affected region,

eastern and southern Africa. Coverage increased from 24% [22-26%] in 2010 to 54% [50-58%] in 2015, reaching a regional total of 10.3 million people (UNAIDS, 2016).

South Africa alone had nearly 3.4 million people on treatment, more than any other country in the world. After South Africa, Kenya has the largest treatment programme in Africa, with nearly 900 000 people on treatment at the end of 2015. Botswana, Eritrea, Kenya, Malawi, Mozambique, Rwanda, South Africa, Swaziland, Uganda, the United Republic of Tanzania, Zambia and Zimbabwe all increased treatment coverage by more than 25 percentage points between 2010 and 2015 (UNAIDS, 2016).

Treatment coverage in Latin American and the Caribbean reached 55% [47-64%] in 2015. In the Asia and Pacific region, coverage more than doubled, from 19% [17-22%] in 2010 to 41% [35-47%] in 2015. Western and Central Africa and the Middle East and North Africa also made important gains but achieved lower levels of coverage in 2015, 28% [23-34%] and 17% [12-24%], respectively. In eastern Europe and Central Asia, coverage increased by just a few percentage points in recent years to 21% [20-23%] - about one in five people living with HIV in the region.

The gains in treatment are largely responsible for a 26% decline in AIDS-related deaths globally since 2010, from an estimated 1.5 million [1.3 million-1.7 million] in 2010 to 1.1 million [940 000-1.3 million] in 2015. The reduction in deaths since 2010 has been greater among adult women (33% decrease) compared with adult men (15% decrease), reflecting higher treatment coverage among women than men, 52% [48-57%] and 41% [33-49%],

respectively. The gender gap for treatment among adults highlights the impact of gender norms that delay initiation of treatment among men, reduce treatment adherence, blunt the preventive effects of treatment, and lead to men accounting for 58% of adult AIDS - related deaths. It is thus obvious that this Fast-Track approach to HIV treatment is working.

Global consensus and leadership have driven greater investment of financial and human capital, and mounting clinical experience and research, improved treatment regimens and diagnostics and reductions in the price of medicines have created gains in efficiency and effectiveness. The continuing momentum reinforces the determination to achieve the 90-90-90 treatment target by 2020, whereby 90% of people living with HIV know their HIV status, 90% of people who know their HIV-positive status are accessing treatment and 90% of people on treatment have suppressed viral loads (UNAIDS, 2016).

Alarmingly though, it is important to note that declines in new HIV infections among adults have slowed remarkably in recent years, with the estimated annual number of new infections among adults remaining nearly static at about 1.9 million [1.7 million-2.2 million] in 2015. Beneath this global figure lie multiple disparities - across regions, within countries, between men and women and young and old, and among specific populations being left behind. These disparities must be addressed in order to achieve the reductions required to end the AIDS epidemic as a public health threat by 2030.

The 2016 UNAIDS update also reveals that the largest reduction in new adult HIV infections occurred in Eastern and Southern Africa. There were about 40 000 fewer new adult HIV infections in the region in 2015 than in 2010, a 4%

decline. More gradual declines were achieved in the Asia and Pacific region and Western and Central Africa. Rates of new adult HIV infections were relatively static in Latin America and the Caribbean, western and central Europe, North America and the Middle East and North Africa, while the annual numbers of new HIV infections in Eastern Europe and Central Asia increased by 57%.

All in all, complex and varied social, structural and economic dynamics within countries account for the uneven geographical distribution of HIV. In many countries, HIV prevalence is higher in cities, where the vibrancy, stress and anonymity of urban life, and its bustle of encounters and interactions, provide increased opportunities for behaviours and sexual networking that may increase the risk of HIV infection. Increased efforts to collect and analyse subnational data are revealing where HIV infections are occurring and where there are gaps in the provision of HIV services.

Particularly, adolescent girls and young women aged 15-24 years are at high risk of HIV infection, accounting for 20% of new HIV infections among adults globally in 2015, despite accounting for just 11% of the adult population. In geographical areas with higher HIV prevalence, the gender imbalance is more pronounced. In sub-Saharan Africa, adolescent girls and young women accounted for 25% of new HIV infections among adults, and women accounted for 56% of new HIV infections among adults. Harmful gender norms and inequalities, insufficient access to education and sexual and reproductive health services, poverty, food insecurity and violence, are at the root of the increased HIV risk of young women and adolescent girls. Also, certain populations at higher risk of HIV infection are not benefiting equitably from ART, including people who inject drugs, men who have sex with men, transgender people and

sex workers. Stigma, discrimination and punitive laws are denying these key populations the multiple benefits of ART. In some regions, including the WHO African Region, men eligible for ART are less likely than women to receive it.

2.7 Treatment cascade for HIV/AIDS

The main steps in the treatment cascade involve diagnosing HIV infection, linking people who take an HIV test to treatment and prevention services, enrolling and retaining people in pre- antiretroviral therapy (ART) care, initiating ART, ensuring long-term adherence and ultimately achieving and maintaining viral load suppression. Programme coverage is improving in all regions, but significant proportions of people still drop out of care at each step of the treatment cascade. Programmes are identifying new opportunities to improve uptake of testing, reduce the time elapsing before eligibility is assessed and treatment is initiated, and support adherence and retention in care. The WHO treatment framework provides a lens for identifying opportunities for improvement at every step, with a focus on adapting service delivery, optimizing treatment regimens and diagnostics, reducing costs and mobilizing communities. Early HIV testing is the first step in the pathway to successful HIV care.

The WHO's 2013 guidelines combine recommendations across the continuum of HIV care and prevention programs, including expanding treatment eligibility for HIV-positive pregnant women, mothers, and children. The guidelines include recommendations to provide lifelong antiretroviral therapy (ART) for all HIV-positive pregnant and breastfeeding women in order

to prevent mother-to-child transmission (PMTCT) of HIV. According to the WHO, providing lifelong ART for all HIV-positive pregnant and breastfeeding women, also known as Option B+, will boost PMTCT services and increase the likelihood that infants born to HIV-positive mothers will be born HIV-negative. In addition, lifelong ART may significantly improve the health and livelihood of HIV-positive pregnant women and mothers and prevent the spread of infection to their partners.

2.8 WHO treatment options for HIV/AIDS

Option A, Option B, and Option B+ are all approaches for utilizing antiretroviral medicines (ARVs) to prevent mother-to-child transmission of HIV, also called perinatal or vertical transmission, which occurs when HIV is transmitted from an HIV-positive woman to her baby during pregnancy, labor and delivery, or breastfeeding. Under Option B+, there is a commitment to provide lifelong ART for life for all HIV-positive pregnant and breastfeeding women, regardless of CD4 count. During pregnancy and for the duration of the breastfeeding period, Options B and B+ are essentially the same. However, under Option B, only women with low CD4 counts or advanced disease are eligible to receive lifelong ART.

Option B+ simplifies the ART regimen to one pill once a day making it much easier for the patient to take and far easier to implement (CDC, 2013). Women with higher CD4 counts take medication from 14 weeks of pregnancy only through childbirth (non-breastfeeding) or until one week after all breastfeeding has finished. ART would be restarted when a woman either

becomes pregnant again or she meets the criteria for initiating treatment for her own health. In the 2013 WHO antiretroviral (ARV) guidelines, several terminology changes were introduced in line with the revised guidelines, including moving away from Option “B” and “B+” to “providing lifelong antiretroviral therapy (ART) to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage” or “providing ART for pregnant and breastfeeding women with HIV during the mother-to-child transmission risk period and then continuing lifelong ART for those women eligible for treatment for their own health (UNAIDS, 2013). While other African countries, including Ghana have adopted Option B+, other countries are yet to adopt it.

2.9 The 4-pronged approach to PMTCT in Ghana

The Prevention of Mother-to-Child Transmission of HIV (PMTCT) intervention is an integrated health service intervention which is offered to mothers and their children to reduce the risk of HIV transmission from the mother to the infant, protect them from HIV-related risk, enhance early case detection and treatment of those infected and to keep those who are HIV negative uninfected. Mother to child transmission of HIV (MTCT) can occur during pregnancy, labour, delivery and breast feeding (GHS, 2014). Interventions required for prevention are aimed at dealing with risk factors during these periods (GHS, 2014). The four pronged approach utilized involves: primary prevention of HIV infection; prevention of unintended pregnancy among HIV-infected women; prevention of HIV transmission from women

infected with HIV to their infants; and provision of treatment, care, and support to women infected with HIV, their infants, and their families.

2.10 Adverse birth outcomes

Despite recent advances in medicine, the incidence of adverse birth outcomes appears to be rising across the world (Kim & Cizmada, 2007). A growing body of literature contends that adverse birth outcomes are a result of harmful environmental exposures (UNAIDS, 2013). Infant mortality (IM), an important health outcome during the first year of life, is unequally distributed across countries at a global level (Kim & Saada, 2013). Although the placenta was once thought to serve as a barrier between the fetus and the outside environment, recent research indicates that the fetus is directly vulnerable to external harm during critical stages of development (Kim & Cizmada, 2007). Attention should not be limited to fetal protection, however, as harmful exposures to the pre-conceptive mother and father may come to affect the development of the fetus later.

The most well-known adverse birth outcomes include: pre-term births, low birth weight, congenital abnormalities (birth defects), pregnancy loss (miscarriage) and neurodevelopmental defects. The period of gestation is a crucial determinant of an infant's health and survival for years to come (United States Environmental Protection Agency [USEPA], 2013). Two measures that may be used to understand the quality of an infant's gestation are the length of gestation (pregnancy length) and birth weight. Normal term pregnancies last between 37 and 41 completed weeks, allowing for more complete development

of an infant's organs and systems. An infant is considered preterm if he or she is born before 37 completed weeks of gestation.

Birth weight is a composite determined by two factors: length of gestation and fetal growth (the rate at which an infant develops and increases in size). Infants may be born with a low birth weight simply because they were born prematurely, or they may be smaller than expected given their gestational age. Low birth weight is considered as less than 2,500 grams. Because birth weight alone does not always indicate whether an infant's fetal growth has been restricted, other measurements such as birth length, head circumference, and abdominal circumference are also used. Other adverse birth outcomes include high birth weight, neonatal mortality, and birth defects, a specific group of adverse birth outcomes that include structural and functional abnormalities.

Birth defects, another group of adverse birth outcomes, though rare in most cases, are a leading cause of infant mortality across the world (Kim & Saada, 2013). Most children who are born with major birth defects and survive infancy are affected physically, mentally, or socially and can be at increased risk for morbidity from various health disorders. Because birth defects have a substantial public health impact on mortality, morbidity, disability, and health care costs there has been a growing interest in defining their causes and in developing, implementing and evaluating prevention programs (Kim & Cizmadia, 2007). Public health surveillance systems for birth defects play an important role in collecting and analyzing data on birth defects in human populations and enable us to learn about occurrence patterns (Kim & Saada, 2013).

This knowledge is essential in identifying the causes of birth defects, informing health policy decisions, and developing and evaluating prevention programs. The Metropolitan Atlanta Congenital Defects Program (MACDP) is a population-based birth defects surveillance program created in 1967 following the thalidomide tragedy. MACDP is designed to provide early warning of increases in the prevalence of defects by monitoring trends over time. Founded as a collaboration of the Centers for Disease Control and Prevention (CDC), Emory University, and the Georgia Mental Health Institute, and administered by CDC, MACDP has been collecting, analyzing, and interpreting birth defects surveillance data on an ongoing basis (Correa-Villaseñor et al., 2003). Case subjects not included in MACDP are children with functional or metabolic disorders (e.g., cerebral palsy or phenylketonuria), hematological disorders (e.g., sickle cell disease, thalassemia, or hemophilia), minor defects (e.g., preauricular tags), and normal variants. Nevertheless, if a child has one or more major defects, then all defects, major and minor, and the presence of metabolic conditions are recorded because information on all defects can be helpful in the recognition of syndromes or patterns of multiple congenital anomalies (CDC, 1979).

2.11 Maternal factors and adverse birth outcomes

Women infected with HIV may have other behaviors that place them at risk for adverse pregnancy outcome, making it difficult to separate the independent roles of non-HIV associated factors and those more directly related to HIV, such as uncontrolled viral replication and immunosuppression (Lambert et al., 2000). Antenatal use of cigarettes, alcohol, illicit drugs, obstetric history and complications are also risk factors for adverse birth outcomes (Abubakari,

Kynast-Wolf, & Jahn, 2015). Thus, adverse birth outcomes, such as low birthweight, preterm delivery, and small size for gestational age, have multiple causes that are not well understood but associated risk factors have been reported to include short maternal height, low or high body-mass index, uterine or placental abnormalities, illicit drug use, low socioeconomic status, smoking, unintended pregnancy, psychosocial stress, previous preterm delivery, infections, and multiple pregnancy (Bagkeris et al., 2015).

In a recent study in Italy, scientists reported the successful use of dolutegravir-based potent combination anti-HIV therapy (ART) to prevent HIV transmission from mother to child while also indicating that there were no birth defects detected in the infant. The scientific community was however cautioned over the conclusions drawn on this breakthrough since, the scientists indicated, much more research analysing other pregnancies will be needed to determine the safety of dolutegravir in pregnancy (Canadian AIDS Treatment Information Update [CATIE], 2016). Thus, as with other small scale studies, data from many HIV- positive pregnant women is needed before the safety of dolutegravir in pregnancy is completely known.

Other studies performed before widespread use of atripla [such as tenofovir (TDF)+lamivudine (3TC)/emtricitabine (FTC)+efavirenz (EFV)] in pregnancy found increased risk of adverse birth outcomes among women initiating 3-drug ART compared with zidovudine (ZDV) in pregnancy. There is however limited data for the risk of adverse birth outcomes with atripla (Zash et al., 2013). According to Zash et al. (2016) there exist a high prevalence of adverse birth outcomes in Botswana, particularly among HIV-infected women. For instance, compared with women initiating other 3-drug ART in pregnancy

(at CD4 < 350) and with women initiating ZDV in pregnancy (at CD4 >350) they found that TDF/FTC/EFV was associated with a decrease in overall adverse birth outcomes while and a corresponding decrease in infants born small for gestational age as well as an increased risk of preterm delivery or stillbirth (Zash et al., 2013).

This study also recognized the need for large studies to evaluate earlier infant outcomes and neural tube defects using women on different ART regimens at conception. Antiretroviral drug resistance and timing of ART have also been identified as factors that require intensive research to ascertain their exact impact on adverse birth outcomes while the role of residual maternal factors as strong correlates for adverse birth outcomes among women on ART has become a serious topic for scientific discourse (Merwe et al., 2011; Paredes, Marconi, Lockman, Abrams, & Kuhn, 2013).

2.12 ART and birth outcomes

In 2012, WHO commissioned several reviews of ARV toxicity and adverse birth events. The WHO, the United States President's Emergency Plan for AIDS Relief, the United States Centers for Disease Control and Prevention and the United States National Institutes of Health are supporting the establishment of ARV pregnancy registries and birth defect surveillance programmes in Malawi, South Africa and Uganda. Other surveillance programmes have been established in Côte d'Ivoire (to monitor TDF use), Kenya (to monitor overall drug toxicities in adults and children living with HIV), Vietnam (to monitor EFV and TDF toxicity among people who use ARV

medicines mainly to prevent HIV infection, such as in serodiscordant couples) and the Lao People's Democratic Republic (focusing on AZT and NVP). Data from these and other initiatives will help to support improvements in the quality of care and help guide future drug regimen choices.

2.13 ART and seropositivity

Perinatal HIV refers to transmission of the virus from an HIV-positive mother to her child during gestation, labor and delivery, or after delivery as a result of breast feeding. It would seem that a child born to an HIV-positive mother is doomed to contract the virus, but an HIV-positive mother does not automatically transfer the virus to her child (Bailey, 2010). When HIV is diagnosed before or during pregnancy, perinatal transmission can be reduced to less than 1% if appropriate medical treatment is given, the virus becomes undetectable, and breastfeeding is avoided. Since the mid-1990s, HIV testing and preventive interventions have resulted in more than a 90% decline in the number of children perinatally infected with HIV (CDC, 2014).

The number of children born annually with HIV has almost halved since 2009 - down from 400 000 in 2009 to 240 000 in 2013. But intensified efforts will be required to reach the global target of less than 40 000 new child infections per year by 2015 (WHO, 2014). In fact, the WHO's impact indicators require that: new paediatric HIV infections due to mother-to-child transmission of HIV are less than 50 cases per 100 000 live births; and mother-to-child transmission rate of HIV is less than 5% in breastfeeding populations or less than 2% in non-breastfeeding populations. Although perinatal transmission is

not perfectly understood, newborns have only about a 25% chance of contracting HIV during gestation (UNAIDS, 2013). Most babies who contract the virus perinatally do so during labor and delivery (70% to 75%) (UNAIDS, 2013).

The low transmission rates from mother to child are the result of the nature of HIV infection and transmission. When HIV enters a person's bloodstream, his or her immune system reacts by producing antibodies to fight the virus (Lambert et al., 2000). Since newborns keep their mother's antibodies until they produce their own antibodies at around 18 months of age, a positive neonatal HIV test result reveals the presence of maternal antibodies that indicate exposure to the virus, not necessarily infection by the virus (Lambert et al., 2000). A baby born to an HIV-positive mother will thus always test positive for HIV, whether that newborn is truly seropositive or not. If the virus did not infect the baby, the baby will eventually lose its mother's antibodies and test negative for HIV. Diagnosis of HIV infection in newborns can be made during the first weeks of life using virologic assays, specifically HIV-1 DNA or RNA assays (Bailey, 2010).

Efforts to interrupt transmission have focused on the use of antiretroviral therapy. Zidovudine has been shown to reduce significantly vertical HIV transmission when used antepartum and intrapartum by the mother and postpartum by the newborn for 6 weeks. However, zidovudine monotherapy increases the risk of developing zidovudine resistance and may jeopardize the goal of durable viral suppression and allow HIV disease progression in the mother and transmission to the infant. Potent antiretroviral therapy is now

recommended for all HIV-infected pregnant women using the same criteria for non-pregnant individuals (McGowan & Shah, 2000).

If possible, combination antiretroviral regimens should include the use of zidovudine but not at the expense of long-term viral suppression. The use of elective Caesarean section should probably be reserved for women who fail to achieve viral suppression at the time of delivery or if indicated for obstetrical reasons. The practice of breastfeeding has been shown to diminish the long-term efficacy of perinatal antiretroviral therapy. All HIV-infected mothers should avoid breastfeeding the newborn if possible.

Therapeutic strategies for HIV infection in pregnancy must be planned with three goals in mind: to maximize prevention of HIV transmission to the greatest proportion of newborns; to utilize ART that will be potent and durable to prevent HIV disease progression and development of drug resistance in the mother; and to time ART optimally for the minimum exposure necessary to provide both safety and efficacy (UNAIDS, 2013). Early identification of HIV infection in the mother is important to maximize maternal options and allow optimal timing of therapy. The role of adjunctive therapies, such as elective Caesarean section, vitamin supplementation and antiseptic washes, requires further study. Understanding the risk factors which underlie mother–infant HIV transmission may lead to development of novel approaches that may be applicable for large-scale, inexpensive deployment. Long-term follow-up of perinatally ART-exposed children and heightened vigilance for morbidity are essential (UNAIDS, 2013).

2.14 ART, birth weight, gestational age and still birth

There are several studies that confirm the risks or adverse outcomes associated with ARV usage (Arts & Hazuda, 2012) and these outcomes include low birth weight (LBW) and pre-term deliveries (PTD) among HIV-positive women on ART. Growing evidence in published literature suggests that ART might be causing adverse birth outcomes among pregnant women in developing countries (UNAIDS, 2013). There is thus a need to consider regimen types for HIV-infected pregnant women (Alemu et al., 2015). Alemu et al. (2015) also suggest the need to design large cohort studies in different countries to ascertain this trend.

LBW and PTD are widely acknowledged global causes of perinatal morbidity and mortality. The debate as to the role of maternal HAART as a risk factor for adverse pregnancy outcome is still ongoing (Areechokchai et al., 2009).

For instance, a 2007 systematic review by Kourtis based on 14 cohort studies reported that ART during pregnancy did not increase the risk of premature delivery, odds ratio (OR) [1.01, 95% (CI) 0.76–1.34]. In subgroup analyses, the use of ARTs containing protease inhibitor (PI) resulted in an OR for premature delivery of 1.24 (95% CI 0.76–2.02), compared to combinations without PI. Compared to therapy initiation in the second trimester and beyond, the initiation of combination therapy before pregnancy or in the first trimester showed an OR of 1.71 (95% CI 1.09–2.67) of PTD. However, their review showed a large degree of heterogeneity (Kourtis et al., 2007).

A UK and Ireland based study reported prematurity rate was higher in women on HAART (14.1%) than in women on mono/dual therapy (10.1%) even after adjusting for ethnicity, maternal age, clinical status [AOR = 1.51, 95%(CI), 1.19-1.93]. Delivery at <35 weeks was more strongly associated with HAART [AOR = 2.34; 95% CI, 1.64-3.37]. The effect was the same whether or not HAART included a protease inhibitor. In comparison with exposure to mono/dual therapy, exposure to HAART was associated with LBW standardized for gestational age ($P < 0.001$), and an increased risk of stillbirth [AOR = 2.27; 95% CI, 0.96-5.41] (Townsend et al., 2007). However, another cohort study reported the incidence of LBW and PTD, respectively, was 9.6% and 7.4%. There was no statistically significant increased risk of LBW [(AOR), 1.5 (95% CI), 0.7-3.2] or preterm birth (AOR, 1.1; 95% CI, 0.5- 2.8) among women who received HAART/PI compared to women receiving 1-2 Nucleoside Reverse Transcriptase Inhibitors (NRTI) (Szyld et al., 2006).

A South African based study showed that 27% of HAART-unexposed infants had LBW compared to 23% of early HAART-exposed infants and 19% of late HAART-exposed infants ($p = 0.05$). In the early HAART group, a higher CD4 cell count was protective against LBW (AOR 0.57 per 50 cells/mm³ increase, 95% CI 0.45-0.71, $p < 0.001$) and PTD (AOR 0.68 per 50 cells/mm³ increase, 95% CI 0.55-0.85, $p = 0.001$), with early nevirapine and efavirenz-based regimens having the strongest associations with preterm birth (AOR 5.4, 95% CI 2.1-13.7, and AOR 5.6, 95% CI 2.1-15.2, respectively). Studies from Cote d'Ivoire and Thailand report similar findings (van der Merwe et al., 2011; Ekouevi et al., 2008; Asavapiriyant & Kasiwat, 2011).

A study done in Botswana in a reasonably large number of subjects, 32,113 women, reported that those continuing HAART from before pregnancy had higher odds of PTD [AOR= 1.2; 95% CI, 1.1-1.4], small for gestational age (AOR=1.8; 95% CI, 1.6, 2.1) and still birth (AOR=1.5; 95% CI, 1.2, 1.8) than those who start later or are on prophylaxis. Among women initiating ART in pregnancy, HAART use (compared with zidovudine) was associated with higher odds of PTD (AOR, 1.4; 95% CI, 1.2, 1.8), small for gestational age (AOR, 1.5; 95% CI, 1.2, 1.9), and still birth (AOR, 2.5; 95% CI, 1.6, 3.9) (Chen et al., 2012). In another study, congenital defects were seen in 7.6% infants on HAART (Nielsen-Seines et al., 2012). These varied reports require country specific research data to support public health policy directives especially in sub-Saharan Africa where such data is very rare.

2.15 ART and toxicity

Although the success of therapy is unquestioned, many issues remain. Since HIV cure is not yet possible, treated people have to maintain lifelong adherence and face the risk of delayed drug toxic effects (Palmisano & Vella, 2011). Furthermore, even when HIV infection is well controlled, chronic low level viremia and inflammation can persist, along with a higher than expected risk for many complications often associated with ageing. This represents a challenge for many healthcare systems, because the amount of resources needed for effective HIV care is likely to increase in the next future. Thus, political

leaders should realize that the epidemic is far from being curbed, rather it is only changing its face (Palmisano & Vella, 2011).

The WHO's reviews on toxicity reveal adverse toxic effects of ARVs. For instance, a WHO review notes that for tenofovir disoproxil fumarate (TDF), data on the risk of clinical events such as mortality, renal failure and bone fractures were limited and showed no difference between TDF and comparison drugs. In one clinical trial, less than 1% of the people taking TDF had severe renal disease that could be ascribed to TDF among the nearly 2,500 adults taking this drug. The trial also showed a very low rate of chronic kidney disease (<6% five years after initiating ART). A review of NVP and EFV found that patients on NVP were more than twice as likely as those receiving EFV to discontinue treatment because of adverse events (UNAIDS, 2013).

Among pregnant women, adverse events associated with NVP are no more frequent than observed in the general adult population, and although pregnant women with a high CD4 count may be at increased risk of adverse events, the evidence supporting this association is weak. Finally, a review of the safety of EFV in the first trimester of pregnancy found no evidence of increased risk of birth defects, in line with the findings of previous systematic reviews and technical guidance (UNAIDS, 2013). It is obvious from the wealth of literature reviewed in this proposal that ART might be causing adverse birth outcomes among pregnant women in developing countries.

The implications of all the available evidence support an association between symptomatic HIV disease, AIDS and adverse pregnancy outcomes (Alemu et al., 2015; Bagkeris et al., 2015). The results of this study will undoubtedly address an important evidence gap on the evolution of and risk

factors for adverse pregnancy outcomes in the sub-Saharan African population. The findings will also reinforce the importance of ensuring improved perinatal outcomes in general and most especially HIV-positive women. Finally, the study will also provide strong scientific basis for the public health policy makers to consider the most appropriate regimen types for HIV-infected pregnant women.



CHAPTER 3

METHODOLOGY

3.1 Study design

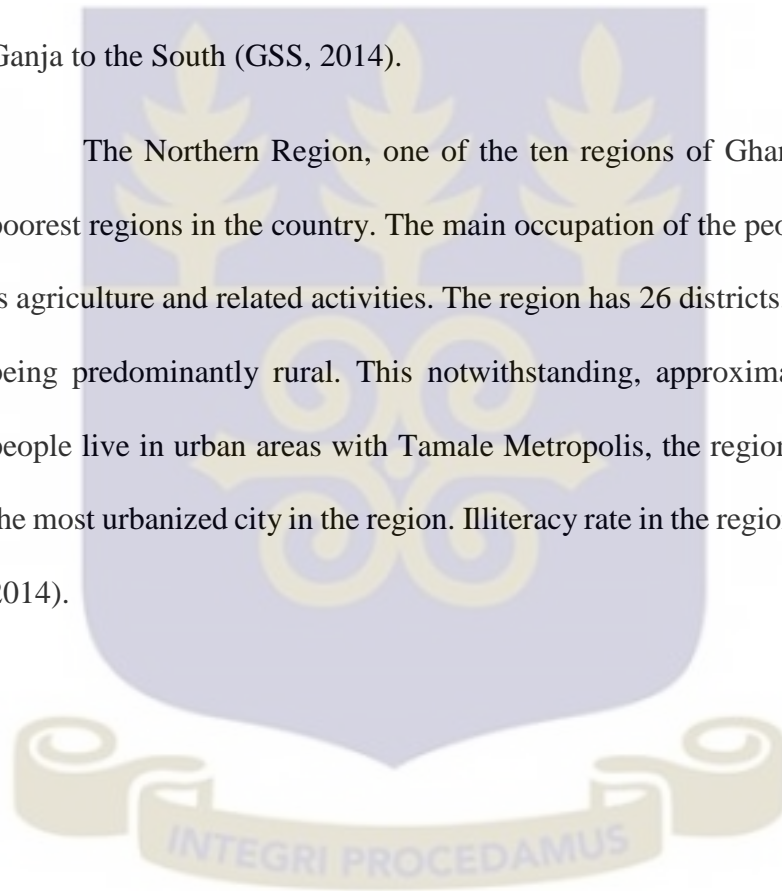
This study was a retrospective study of HIV positive women who received ART at the TTH between 2010 and 2015. The distinguishing feature of this design is the fact that the investigator conceives the study and begins identifying and enrolling subjects after outcomes have already occurred. The investigator has to go back to preexisting data that was not necessarily acquired in a precise, predetermined way. Its limitation is thus, follow up may have been incomplete.

3.2 Study area

The study was conducted at the Tamale Teaching Hospital (TTH). The TTH is a referral centre for antiretroviral treatment in Tamale, the capital city of the Northern Region of Ghana. Tamale is located in the Tamale Metropolitan Assembly (TaMA), an assembly that was elevated to the status of a Metropolis in 2004. The Metropolis is one of the six Metropolitan Assemblies in the country and the only Metropolis in the three Northern Regions of Ghana namely; Upper East, Upper West and Northern Regions. It lies between latitude 9.16° and 9.34° North and longitudes 00.36° and 00.57. The Tamale Metropolitan Assembly is located approximately 180 metres above sea level (Ghana Statistical Service [GSS], 2014).

The topography is generally rolling with some shallow valleys which serve as stream courses. There are also some isolated hills but these do not inhibit physical development. The Tamale Metropolis is one of the 26 districts in the Northern Region (GSS, 2014). The Metropolis is located in the central part of the Northern Region and shares boundaries with five other districts namely the Savelugu- Nanton to the North, Yendi Municipal Assembly to the East, Tolon-Kumbungu to the West, Central Gonja to the South West and East Gonja to the South (GSS, 2014).

The Northern Region, one of the ten regions of Ghana, is among the poorest regions in the country. The main occupation of the people in the region is agriculture and related activities. The region has 26 districts, with 24 of them being predominantly rural. This notwithstanding, approximately half of the people live in urban areas with Tamale Metropolis, the regional capital, being the most urbanized city in the region. Illiteracy rate in the region is 62.8% (GSS, 2014).



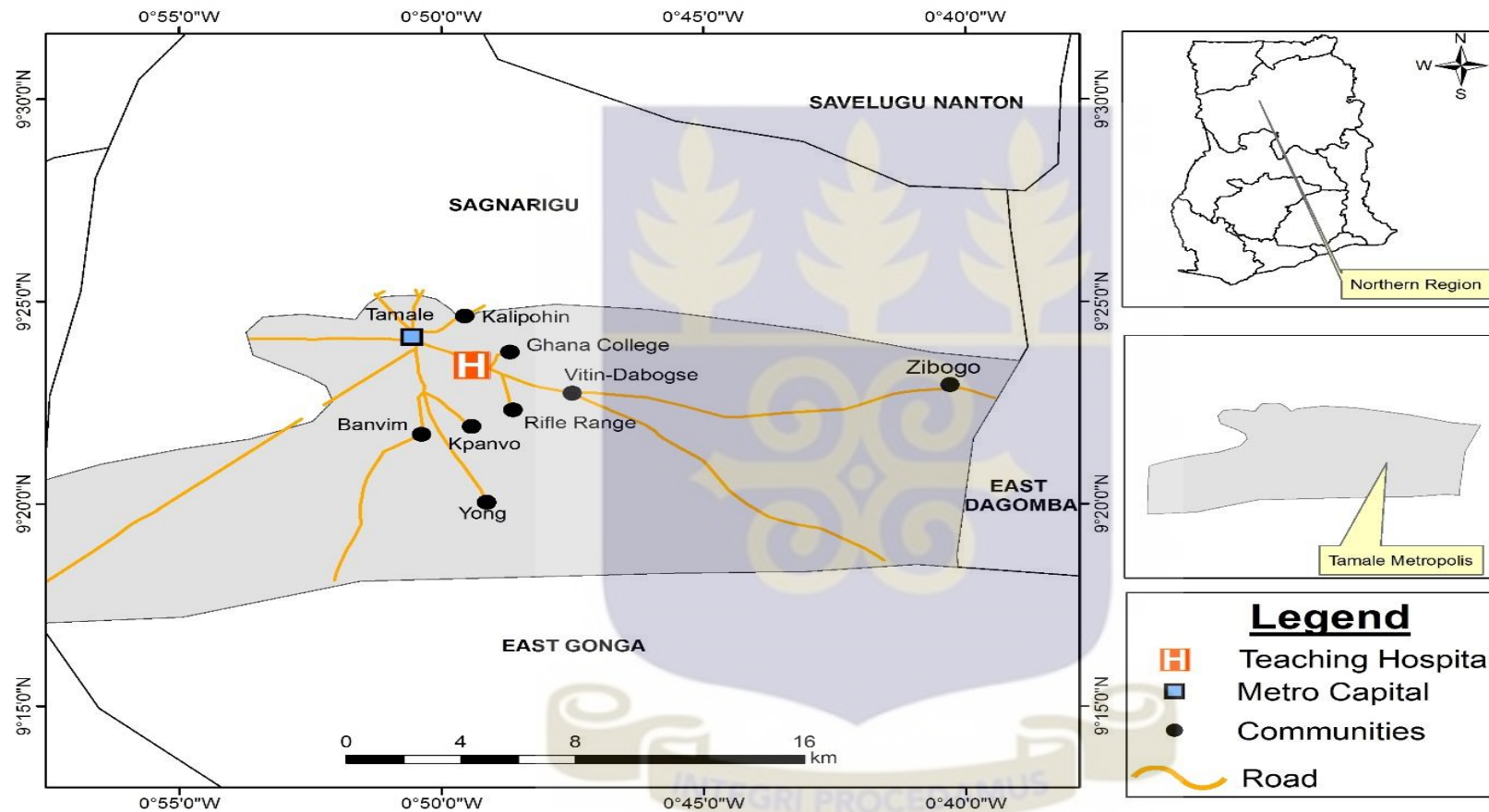


Figure 2. A map of the Tamale Metropolis, Ghana (Designed by the GIS Unit, Department of Geography and Regional Planning, University of Cape Coast, 2016)

3.3 Study population

The study population was extracted from TTH's PMTCT registry with the aim to obtain birth outcomes data. HIV positive pregnant women under ART to term at the TTH between 2010 and 2015 were considered for this study. As expected, the hospital had strict regulations regarding the release of sensitive patient data and statistics for a vulnerable group as HIV clients and it was thus impossible to get exact estimates of the patient numbers visiting the ART clinic until ethical clearance was granted by the ERC of the GHS.

3.4 Inclusion and exclusion criteria

Only singleton newborns were considered for this study. Clients who had twins at birth were thus excluded from the study. For women who had multigravida, only data for the first child (primigravida) was used in this study to ensure consistency. All women should have been on ART throughout the period of pregnancy (first trimester to third trimester). The study also excluded all clients who were transferred from different ART clinics to TTH. Women who did not know the date of their last menstruation or did not have an obstetrical ultrasound examination during the first trimester were excluded as PTD would then be difficult to estimate in such cases.

3.5 Sampling

The purposive sampling technique was used to extract data from TTH's registry. The choice of a purposive sampling technique was based on issues of difficulty in obtaining numbers from such a rare and vulnerable population as

well as the nature of the study questions. This sampling method ensured that the investigator, upon clearance by the ERC of the GHS and the NACP, reviewed all relevant records where available until completeness and saturation was realized. Therefore, insistence on data completeness and saturation helped reduce any biases while the representativeness of the study was greatly enhanced.

Thus, the investigator thoroughly assessed the feasibility of using quantitative studies with probability based methods but the following reasons appealed to the use of the purposive sampling method – [1] the research question called for an intensive investigation of a small available population of ART recipient pregnant women and [2] the investigator was performing a preliminary, exploratory study. In this regard, the investigator placed much regard on completeness when what was obtained from all relevant records provided an overall sense of the meaning of birth outcomes. The investigator also prioritized saturation in this case when he gained confidence that he was learning little that was new from subsequent record reviews. Adhering to these guidelines undoubtedly helped ensure that the purposive sample adequately represented the setting or issues studied.

Based on hospital records available, data on all eligible HIV-positive women who received ART from the TTH between 2010 and 2015 were reviewed in order to extract birth outcomes information. This information comprised newborn's HIV status, birth weight, preterm delivery, still birth, APGAR score and congenital anomalies (assessed per the guidelines of the Metropolitan Atlanta Congenital Defects Program [MACDP]). This is a non-probability sampling method in which ART recipient pregnant women's

medical records were selected for a purpose, because of their unique position. Considering the limitations such as a lack of resources, a limited number of ART clients as well as the short time period for the study (two months), this method was found useful over the probability sampling techniques.

3.6 Data collection and procedures

A checklist containing maternal characteristics and birth outcomes was used to collect data from the TTH. Information required for maternal characteristics included: age, nationality, religion, educational level, gravidity, type of HIV, type of ARV combination, time of initiation of ART, coinfections, mode of delivery, smoking history and history of alcohol or substance abuse. Newborn characteristics that were elicited include: HIV status, birth weight, preterm delivery, still birth, APGAR score and congenital anomalies as per the Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines. These deformities were categorized as cardiovascular, genitourinary, musculoskeletal, craniofacial and central nervous system (CNS) disorders.

Since staff of the GHS are trained to appreciate the purpose of patient data confidentiality, the investigator employed the services of staff nurses at TTH to enter relevant data from the patients' records into the study instruments or checklists. Only identity codes were used so as to keep patient names anonymous. Data obtained were subsequently handed over by nurses to the Principal Investigator who then forwarded them to the statistician for further analysis. The complete list of names and codes would be made available only to the Principal Investigator for purposes of future professional or supportive

recommendations on respective clients. This list would be required only after data analysis where justifiable implementations of study recommendations become appropriate.

3.7 Ethical considerations

This study obtained approval from the Ethical Review Board of the Ghana Health Service. Written permission was also obtained from the Research and Development Division of the Tamale Teaching Hospital (TTH). More so, a data sharing agreement plan was signed by the Principal Investigator and the Ghana National AIDS/STI Control Programme (NACP) and this allowed the investigator limited access to appropriate datasets from the NACP. This study pertains to some future planning, preventive, or therapeutic initiatives which may benefit the patients whose records were studied or may benefit patients of similar background in the future. Therefore, with regard to the element of beneficence, contact would be made with respective patients where possible (as may be practically difficult to trace some living or dead) if the results of research findings suggest that ART recipient mothers or their children be followed up for further counselling or other professional support services. Where possible, identifiers would be removed from the parts of the record to which researchers have access and where not possible patient identities will be kept strictly anonymous when the results are made public. In fact, collective confidentiality and anonymity of patient data collected is prime to the investigator and staff of the TTH as well as the NACP.

Retrospective reviews of medical records represent an inexpensive and efficient way of gaining a comprehensive view of the health system's response to a particular medical problem while also requiring the use of medical notes beyond the primary purpose for which they were created. Thus, once confidentiality was maintained, medical records review qualified as an effective tool for this important scientific study. In collaboration with the ERC and staff at TTH the investigator struck a balance between the risks to privacy and confidentiality and the potential benefits to existing patients, future patients and the public in general.

In doing this, records were kept securely by the GHS staff in charge at the ART clinic of TTH while the Principal Investigator was always reminded and or instructed about the duty of confidentiality. Also, via the data sharing agreement pact between investigator and the NACP, a strong collaborative effort to ensure confidentiality and data protection is undoubtedly guaranteed. Moreover, only the Principal Investigator and study Statistician had access to data during electronic data management and or storage. The Principal Investigator formally indicated professional responsibility for any breach of confidentiality. Finally, no other relationship, bias or ethical conflict existed which prevented the investigator from evaluating the study solely on its merits.

3.8 Independent variables (Predictors)

The main independent variable was the type of ARV. Other comorbidity factors or possible confounders included the type of HIV, time of ART initiation, coinfections during ART, mode of delivery, history of smoking, and history of alcohol or other substance abuse.

3.9 Dependent variables (expected outcomes)

The main expected outcomes were; HIV status of newborns, preterm deliveries (PTD: < 37 gestational weeks), stillbirths and low birth weight (LBW: <2, 500g). Other expected outcomes were identified based on the guidelines of the Metropolitan Atlanta Congenital Defects Program (MACDP guidelines). These congenital defects included cardiovascular, genitourinary, musculoskeletal, craniofacial and CNS disorders.

3.10 Data analyses

Prior to analyses of data, data quality assurance was ensured through repetitive reviews and editing to check for completeness, consistency, and double-data entry. In addition, supervisory checks were conducted to reconcile any inconsistencies that were detected during second data entry. This was then followed by the generation of a data spreadsheet using Microsoft Excel (2013) followed by importation into the Stata software (StataSE 13.0) for statistical analyses. Data collected included maternal demographic characteristics and obstetric history, as well as ART used including timing of treatment. Primarily,

the infant birth outcomes that were considered include: newborn's HIV status, low birth weight (<2,500 g), preterm delivery (gestational age <37 weeks) and still births, defined as newborns who were dead at birth or were born-alive but died before their first birthday.

Descriptive statistics such as means were then used to describe the ages of women as well as the birth weights of newborns. Frequency distribution tables and bar charts were used to summarize respective demographic and birth outcomes data. Associations between the main independent variable (ARV combinations) and dependent variables (LBW, PTB, HIV status and stillbirth) were examined using the Fisher's exact test (χ^2) since some of the cells contained expected frequencies less than five (5). More so, the one sample *t*-test was used to test the differences between population estimates, mean maternal age and birth weight of newborns.

The original analysis plan for this study was to put factors associated with respective birth outcomes and having a *p*-value below 0.05 into a logistic regression model to identify which factors are independently associated with the birth outcomes. The logistic regression model would be important in such instances as it would have helped establish the strength of the association where there existed significant associations between respective variables. The simple logistic regression model would usually provide crude odds ratios (OR) and 95% confidence intervals (95% CI) arising from the relationships between any one dependent variable and an independent variable. Since this model does not account for other confounders that could impact respective outcomes and hence lacking the ability to deal with such possible confounders, a multiple (adjusted) logistic regression model would have been appropriate to evaluate adjusted odds

ratios and corresponding 95% confidence intervals (95% CI). This way, the logistic regression model would have been a very helpful tool in attempts to establish the strength of the relationship between any independent variable (ARV, HIV type, smoking status, coinfections, etc) and the main dependent variables (LBW, HIV status, preterm delivery and still birth).

In this study however, upon conducting the Fisher's exact test, no significant association was observed in all cases hence no need for a logistic regression model in this analyses. Consequently, in this new plan, LBW was categorized into low birth weight ($<2,500\text{g}$) and normal birth weight ($\geq 2,500\text{g}$). Similarly, preterm deliveries were considered dichotomous/continuous variables comprising a preterm group (gestational age < 37 weeks) and a normal term group (gestational age ≥ 37 weeks). Other birth outcomes such as still births (dead newborns), and newborn's HIV status were analysed as categorical variables. ART exposure (or type of ARV combination) and other independent variables including smoking status of mothers, HIV type, coinfections, etc were considered categorical in nature while mother's age at last birth was treated as a discrete variable. All statistical tests were 2-sided, with p-values less than 0.05 considered statistically significant.

CHAPTER 4

RESULTS

4.1 Flow chart and characteristics of study population

This study cohort comprised 101 ART recipient women at the Tamale Teaching Hospital (TTH). The mean age of these women was 31.3 ± 5.2 years (95% CI, 30.22 – 32.34). The one sample t-test shows that this mean age is significantly higher ($p = 0.018$) than the population estimate of 30 years. Fifteen women received the preferred regimen that is recommended by the WHO as well as the Ghana Health Service (GHS). The preferred regimen is described as a fixed dose of tenofovir + lamivudine + efavirenz (TDC+3TC+EFV). The other eighty-six (86) clients were put on an alternative regimen as first line therapy where the preferred regimen was either unavailable or contraindicating.

These alternative regimens as prescribed by the WHO and Ghana Health Service and received by the women in this study include the following: tenofovir + lamivudine + nevirapine (TDF+3TC+NVP); tenofovir + entricitabine + efavirenz (TDF+FTC+EFV); stavudine + lamivudine + nevirapine (d4T+3TC+NVP); zidovudine + lamivudine + efavirenz (AZT+3TC+EFV); and zidovudine + lamivudine + nevirapine (AZT+3TC+NVP). One client received an alternative regimen comprising only two drugs namely zidovudine + lamivudine (AZT+3TC) because the ART clinic experienced shortage of nevirapine or another non-nucleoside reverse transcriptase inhibitor. The flow chart in figure 3 illustrates the breakdown in numbers of respective clients and birth outcomes data.

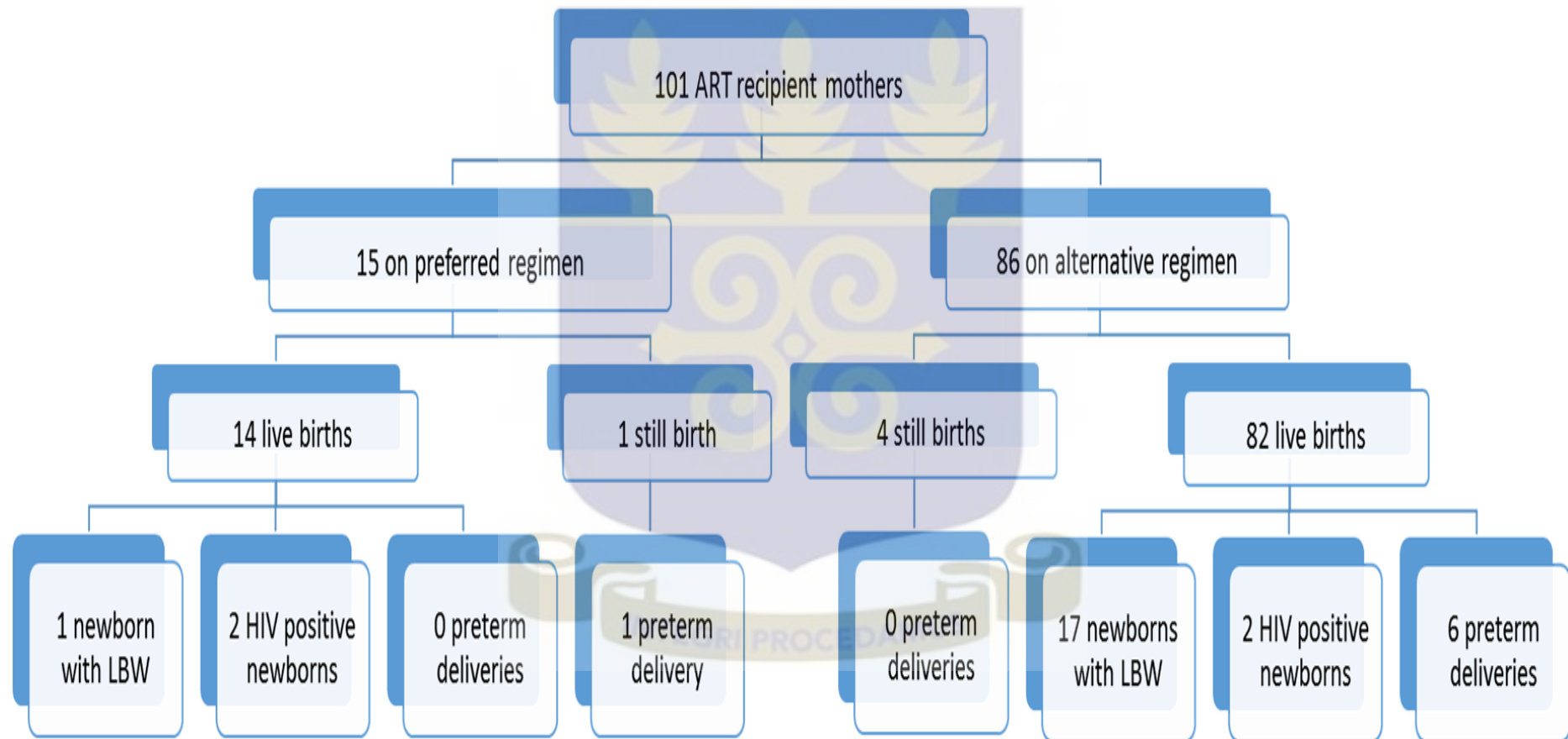


Figure 3. Study flow chart of ART recipient mothers at the TTH from 2010 to 2015

Table 2 provides details of other maternal characteristics such as age, HIV type, education, gravidity, etc. As observed, women between the ages of 21 to 34 represent the most active reproductive group as 73.3% and 66.3% of clients belonging to this age category were put on preferred and alternative regimens respectively. The age category of at least 20 years were the most infertile group as the study recorded 0% and 1.2% of this age group on the preferred and alternative regimens respectively. It appears HIV clients are reproductively very active in their older ages. This observation is justified by those clients aged 35 years and above where 26.7% and 32.6% of them received preferred and alternative regimens respectively.

There were no foreign clients in this study as all 101 clients were Ghanaian. As expected in the Northern Region of Ghana, the study recorded more Muslim clients in comparison with the Christian cohort. While 66.7% of clients on the preferred regimen were muslims, only 33.3% were Christians. Similarly, 62.8% of muslims were placed on alternative regimens as compared to 37.2% of Christian counterparts. About 46.7% of clients on the preferred regimen had basic or secondary education while 26.7% had no formal education with the remaining 26.7% having received some form of tertiary education. A similar trend was observed for clients on alternative regimens as 44.2% of these acquired some basic or secondary education while 40.7% had no formal education. Only 15.1% of clients had acquired tertiary level education at the time of this study.

This study recorded more primigravida women than multigravida women. Over ninety-three percent (93.3%) of the women receiving the

preferred regimen were primigravida while 82.6% on alternative regimens were primigravida. The study found none of the clients presenting with HIV type 2 as all 101 clients presented with HIV type 1. There were also no coinfections reported of the clients in this study.

With regard to the mode of delivery, the clinic undertook very few cesarean sections. Only 13.3% of women on the preferred regimen received cesarean sections during delivery while another 24.4% on alternative regimens were delivered via cesarean section. As the results in table 2 show, though a very limited number, the same women who smoke during pregnancy were the same women who indulged in substance abuse of some kind especially alcohol in the form of hard liquor. The figures respectively show that 6.7% and 2.3% of clients on the preferred and alternative regimens either smoked or were alcoholics.

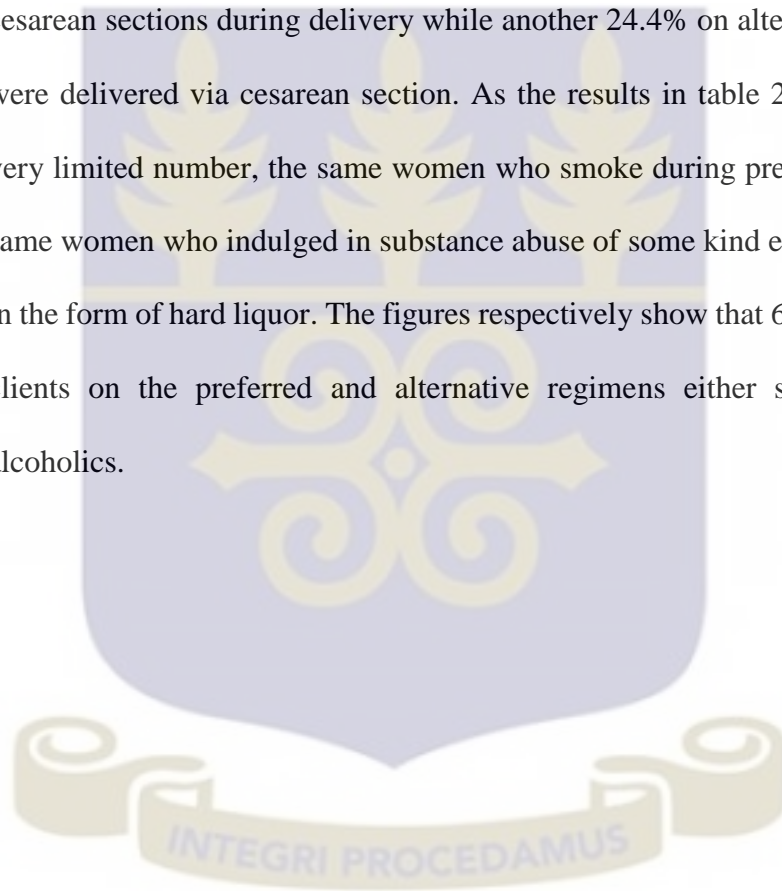


Table 2: Characteristics of clients stratified by antiretroviral drug use (N = 101)

Characteristic	Preferred regimen	Alternative regimen
Age - no. (%)		
≤20	0 (0.0)	1 (1.2)
21-34	11 (73.3)	57 (66.3)
≥35	4 (26.7)	28 (32.6)
Nationality – no. (%)		
Ghana	15 (100.0)	86 (100.0)
Religion – no. (%)		
Muslim	10 (66.7)	54 (62.8)
Christian	5 (33.3)	32 (37.2)
Education – no. (%)		
Non-formal	4 (26.7)	35 (40.7)
Basic	6 (40.0)	26 (30.2)
Senior High	1 (6.7)	12 (14.0)
Tertiary	4 (26.7)	13 (15.1)
Gravidity – no. (%)		
1	14 (93.3)	71 (82.6)
>1	1 (6.7)	15 (17.4)
HIV type – no. (%)		
1	15 (100.0)	86 (100.0)
Coinfections – no. (%)		
Absent	15 (100.0)	86 (100.0)
Mode of delivery – no. (%)		
Cesarean	2 (13.3)	21 (24.4)
Vaginal	13 (86.7)	65 (75.6)
Smoking status – no. (%)		
Non-Smoker	14 (93.3)	84 (97.7)
Smoker	1 (6.7)	2 (2.3)
Substance abuse – no. (%)		
No	14 (93.3)	84 (97.7)
Yes	1 (6.7)	2 (2.3)

4.2 Birth outcomes

In this study, all newborns who died at birth did not have their HIV status or birth weight recorded. Hence, with 96 live births as demonstrated in the flow chart above (figure 3), the mean birth weight of newborns was $2.9 \pm 0.5\text{kg}$ (95% CI, 2.78 – 2.99). The one sample t-test reveals that the mean birth weight in this study is significantly lower ($p = 0.0286$) than the population estimate of 3.0kg. As represented in figure 3, the prevalence of low birth weight was 18.8% (18/96). Five newborns died at birth, resulting in a 5.0% (5/101) prevalence rate of still births. Moreover, HIV seropositivity rate was obtained as 4.2% (4/96) in this study.

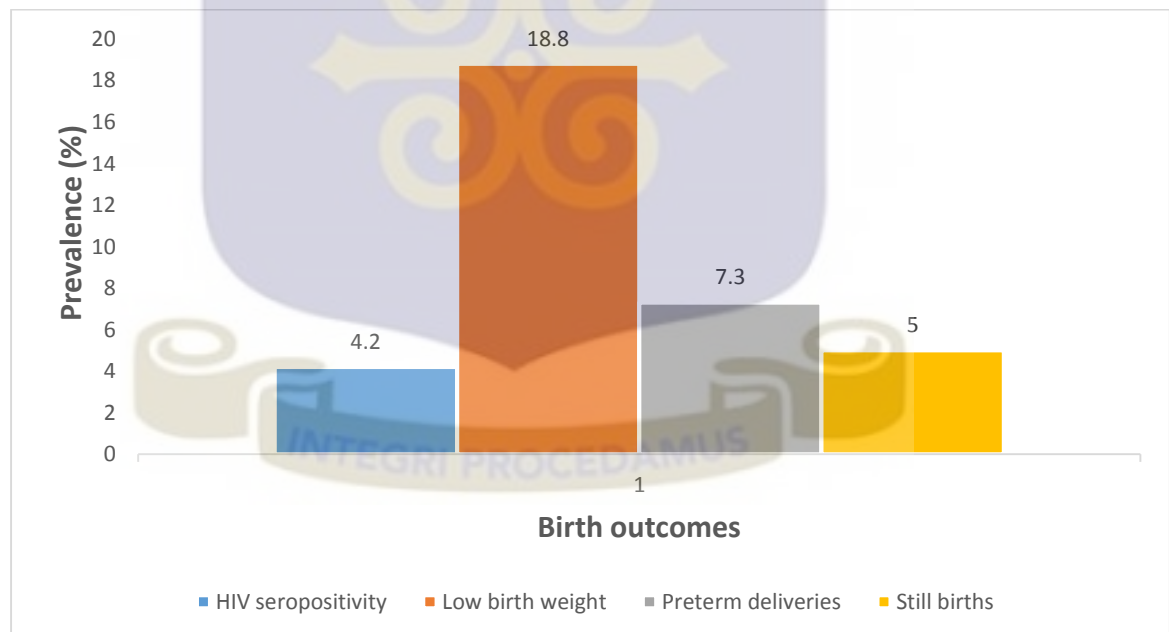


Figure 4: A bar chart showing respective prevalence of key birth outcomes amongst the 101 ART recipient clients

4.3 Association between birth outcomes and ARVs

Table 3 displays results of the Fisher's exact test of association between birth outcomes and the preferred as well as alternative ARV combinations.

Table 3: Association between key birth outcomes and antiretroviral drug use among 101 clients

Outcome	Preferred regimen	Alternative regimen	χ^2	p-value
HIV status – no. (%)				
Negative	12 (85.7)	80 (97.6)	4.203	0.100
Positive	2 (14.3)	2 (2.4)		
Birth weight – no. (%)				
≥2500g	13 (92.9)	65 (79.3)	1.450	0.457
<2500g	1 (1.2)	17 (20.7)		
Gestational age – no. (%)				
≥37 weeks	15 (100.0)	80 (93.0)	1.113	0.588
<37 weeks	0 (0.0)	6 (7.0)		
Still births – no. (%)				
Live born	14 (93.3)	82 (95.4)	0.110	0.560
Stillborn	1 (6.7)	4 (4.7)		

As shown in table 3, this study suggests that no significant association exists between the observed birth outcomes and the respective ARV combinations. Both client groups on the preferred regimen and alternative regimens each recorded 2 cases of HIV seropositive newborns but this is not associated with the type of regimen the women received ($p = 0.10$). Even though, women who received alternative regimens recorded higher cases of low birth weight (17 cases) in comparison to just 1 case in clients on the preferred regimen, the prevalence of low birth weight was not associated with the type of treatment regimen the women received ($p = 0.457$).

Similarly, despite clients on alternative regimens recording 6 cases of preterm deliveries in contrast to none (0 case) from clients on the preferred regimen, preterm deliveries had no association with ARV regimens ($p = 0.588$). This trend continues likewise for cases of still birth where women on alternative regimens recorded 4 still births in comparison to 1 still birth from women who received the preferred regimen, with the resulting test of association showing no link between still births and ARV combinations ($p = 0.560$).

4.4 Association between birth outcomes and a-priori maternal confounders

As illustrated in the conceptual framework to this study, a-priori maternal confounders such as smoking, alcohol abuse, HIV type, coinfections, gravidity, maternal genome, education, religion and mode of delivery have been shown in scientific literature to have a significant impact on adverse birth outcomes in HIV positive women on antiretroviral therapy. Such confirmed scientific evidence drove this study to conduct the Fisher's exact test to determine if the presence of confounding maternal risk factors were significantly associated with birth outcomes observed in this study. The results of this test are shown in table 4 where none of the maternal confounders has been shown to have a significant association with respective birth outcomes.

It is important to note that timing of ART has also been shown to impact adverse birth outcomes significantly. This study however utilized as part of its inclusion criteria, only HIV infected women who started ART in the first trimester through term. Here again, the expected frequencies in some of the cells was less than five (5), and thus appropriate to conduct a Pearson's chi squared test on the data even though the

Pearson's chi squared test showed a significant association between HIV status, birth weight, still birth and smoking or substance abuse ($p = 0.001$, $p = 0.492$ and $p = 0.021$ respectively). These values have been captured in italics in table 3, where the row has been labelled with five (5) bold asterisk (*****).

Table 4: Association between key birth outcomes and maternal risk factors

Outcome	HIV seropositivity	Birth weight	Preterm delivery	Still birth
	χ^2 (p-value)	χ^2 (p-value)	χ^2 (p-value)	χ^2 (p-value)
Age	2.087 (0.329)	1.337 (0.513)	0.760 (0.681)	0.404 (1.000)
Gravidity	0.209 (0.524)	0.492 (0.492)	1.464 (0.241)	0.990 (1.000)
Mode of delivery	1.315 (0.569)	0.647 (0.548)	0.135 (1.000)	1.551 (0.586)
Education	1.751 (0.512)	2.715 (0.438)	2.876 (0.307)	2.942 (0.411)
Religion	0.198 (0.555)	0.789 (0.419)	1.096 (0.411)	1.237 (0.353)
Smoking	10.746 (0.082)	0.471 (1.000)	0.195 (1.000)	5.293 (0.143)
*****	<i>10.746 (0.001)</i>	<i>0.471 (0.492)</i>		<i>5.293 (0.021)</i>
Substance abuse	10.746 (0.082)	0.471 (1.000)	0.195 (1.000)	5.293 (0.143)
*****	<i>10.746 (0.001)</i>	<i>0.471 (0.492)</i>		<i>5.293 (0.021)</i>

***** Selected Pearson's chi square and p values showing significant associations between some birth outcomes and maternal risk factors

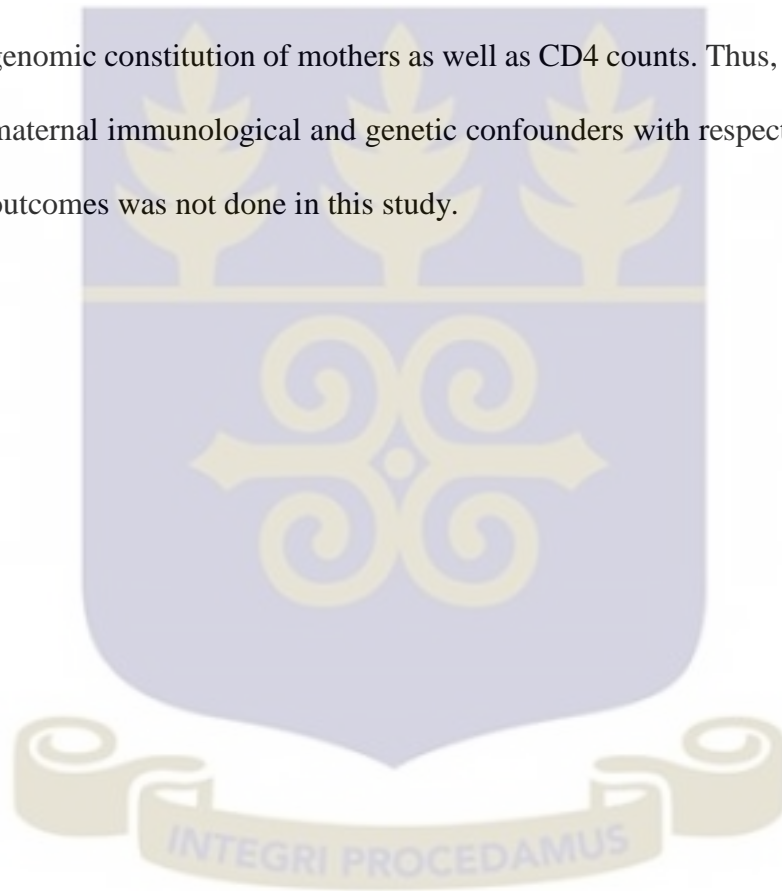
4.5 Limitations to the study

As is common with any retrospective cohort study, recall bias was a major limitation in this retrospective study as some HIV infected mothers found it difficult to recollect key issues relating to their medical history including the presence of coinfections during ART. Another key limitation is the difficulty of several clients to accurately recollect the time of their last menstrual period. Such women were excluded from the study as this data was deemed critical for assessing the prevalence of preterm deliveries.

Due to the limited time frame for this study, it was very difficult and time consuming to trace for data on women who were transferred from other ART clinics to the ART clinic at TTH. Such clients were subsequently excluded from this study. Some of such limitations impacted the volume of data available for this study however small it may have been. Despite been part of this study plan, it was very difficult if not impossible, to acquire relevant data from the labour ward at TTH as there was inefficient data consolidation between the ART clinic and the labour ward. Some of such data include APGAR scores [at 1 and 5 minutes after delivery] and records of congenital defects. Part of the reason is the fact that such data is not of high priority to the ART clinic and so records are not kept on such data at the labor ward.

Attrition was another limitation to this study as several clients on the ART clinic`s register never returned for delivery after at least seven (7) months of receiving ART at TTH. Such clients, as the clinic`s personnel put it, were delivered with the help of traditional birth attendants [TBAs] while others may have delivered at other health facilities for reasons not clearly understood by

clinic staff. It was also difficult to ascertain the level of adherence to ART by the women since most clients would usually take the drugs home for administration. Other key confounders that were difficult to obtain from the mothers were their nutritional statuses while they received ART as well as the specific types of coinfections they may have had while on ART. Finally due to the retrospective nature of this study plus the later adoption of WHO's Option B+ by the Ghana Health Service, it was not feasible to respectively assess the genomic constitution of mothers as well as CD4 counts. Thus, an assessment of maternal immunological and genetic confounders with respect to adverse birth outcomes was not done in this study.



CHAPTER 5

DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.1 Discussion

The findings of this study reveal that birth outcomes are not significantly associated with ART as well as maternal risk factors such as smoking, alcohol and other substance abuse. This makes women on ART more confident about their chances to have children without fear of possible adverse outcomes. Such findings reinforce findings from previous studies revealing that HIV positive pregnant women have become increasingly interested in having babies as treatment with ARVs progresses since these women grow in confidence about available research evidence showing significant declines in adverse birth outcomes due to ART (Li et al., 2015; Myer et al., 2010; Taylor et al., 2013). In fact a recent study in neighboring Burkina Faso has reported increases in pregnancies with increasing exposure to ART (Poda et al., 2016). With older women (≥ 30 years) becoming more interested in having babies, the idea is that such women have grown to trust the effectiveness of ARVs and after a few years, they are able to make a very easy decision to have their own babies. This is due to the fact that ARVs have become very effective at improving the health statuses of pregnant women and their children (Alemu et al., 2015; Li et al., 2015; UNAIDS, 2013). This is further supported by a study that observes not only an increase in the number of ART recipient pregnant women, but also the need to assess timelines in pregnancy with respect to age (Nlend et al., 2014).

The significant reduction in mean birth weight of newborns calls for special attention. Globally, birth weights of newborns to ART recipient mothers has

been a controversial issue for researchers. While some researchers report increases in birth weight as a result of ART, others claim otherwise. In Ghana, a similar study carried out in the same study area among HIV uninfected mothers found a mean birth weight of newborns to be 2.98kg (Abubakari et al., 2015). There is however no significant difference ($p = 0.068$) between this value and the mean birth weight (2.9kg) reported in this study. This suggests that ART in the study area and thus Ghana is very effective at maintaining a relatively healthy infant population.

Another striking finding in this study is the prevalence of HIV seropositivity (4.2%), representing a huge shift from the reported or allowable range of HIV seropositivity of 1-2% (Havens & Mofenson, 2009). Considering the fact that global efforts are being made to eradicate vertical transmissions of HIV, all relevant stakeholders must endeavor to ensure that the preferred regimens are available and that clients adhere strictly to treatment regimens as required. This high prevalence rate is therefore a wakeup call to policy makers if the goals of the Global Plan are to be achieved in the fight against HIV/AIDS.

Low birth weight has been reported as an important predictor of the overall health status of every newborn (CDC, 1979) and is also a measure of the strength of every nation's future populace (Ibrahim & Keefe, 2014). The prevalence rate recorded in this study (18.8%) is lower when compared with a similar study conducted in Adidjan, Ivory Coast where the prevalence of low birth outcome was reported as 22.3% (Ekouevi et al., 2008). It however differs from the 14.2% prevalence reported in a recent study from Burkina Faso (Poda et al., 2016). Similarly, a study in Cameroon provides a prevalence rate of low

birth weight as 11.6% (Nlend et al., 2014). In contrast, a recent study in Tanzania recorded a 16% prevalence rate of low birth weight thus indicating a slightly lower figure from that recorded in this study (Li et al., 2015).

Another study in South Africa stated the prevalence of low birth weight amongst 1228 clients on ART as 22.4% (Merwe et al., 2011). It is thus critical for Ghana to monitor the continuum of ART at the various sentinel clinics to ensure that the country keeps up with the targets of the Global Plan. One study in Ghana has indicated an association between low birth weight and maternal educational status (Tampah-Naah, Anzagra, & Yendaw, 2016) but this study finds no significant association between the two variables.

It is common place to find studies of this nature reporting difficulties in estimating the rate of preterm deliveries as most clients usually cannot remember their last date of menstruation or never had an ultrasound examination in the first trimester of pregnancy. This gap has been filled by this retrospective study in which the prevalence of preterm delivery was recorded as 7.3%. This figure is similar to those reported by other studies in Africa (Li et al., 2015; Poda et al., 2016) but slightly lower than the 9.7% preterm delivery rate reported in Cameroon (Nlend et al., 2014). A rather high figure (29%) has been reported in another study in South Africa (Merwe et al., 2011). Also, the 5.0% still birth rate reported in this study is lower than the figure (6.0%) reported in the study of neighboring Burkina Faso (Poda et al., 2016).

With regards to treatment regimens, it is important to stress the need for Ghana to return to the preferred first line option recommended by the WHO and adopted by the Ghana Health Service (GHS). These guidelines recommend the

use of less toxic and more convenient regimens as fixed-dose combinations for first-line ART. Once-daily regimens comprising a non-thymidine nucleotide/nucleoside reverse transcriptase inhibitor (NRTI) backbone (TDF + FTC or TDF + 3TC) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) (EFV) are maintained as the preferred choices in pregnant women (GHS, 2014; UNAIDS, 2013).

This study did not find any use of protease inhibitors such as ritonavir boosted lopinavir (LPV/r) and ritonavir boosted atazanavir (ATV/r). This gives a positive signal as protease inhibitors are the most implicated regimens for adverse birth outcomes (Havens & Mofenson, 2009). However, this study reveals that most of the clients were put on the alternative regimens despite confirmed scientific evidence suggesting a high risk of adverse birth outcomes associated with some of these alternative regimens. It is a known fact that most areas of the developing world lack access to most of the preferred regimens and even when they become available, clinics quickly run into shortages for long periods of time (UNAIDS, 2013). This is particularly alarming when one considers the positive strides Ghana has made in its efforts to prevent mother to child infections of HIV. Despite no associations between birth outcomes and ARVs, it is clear from the results that women on alternative regimens presented more adverse outcomes in comparison to those women who received the preferred first line regimen.

Another surprising observation in this study is the fact that during the 2010 and 2013 periods, two clients received stavudine (d4T) as part of drug combinations. In 2010, the WHO set guidelines emphasizing the importance of avoiding d4T as a preferred option in first-line regimens because of its well-

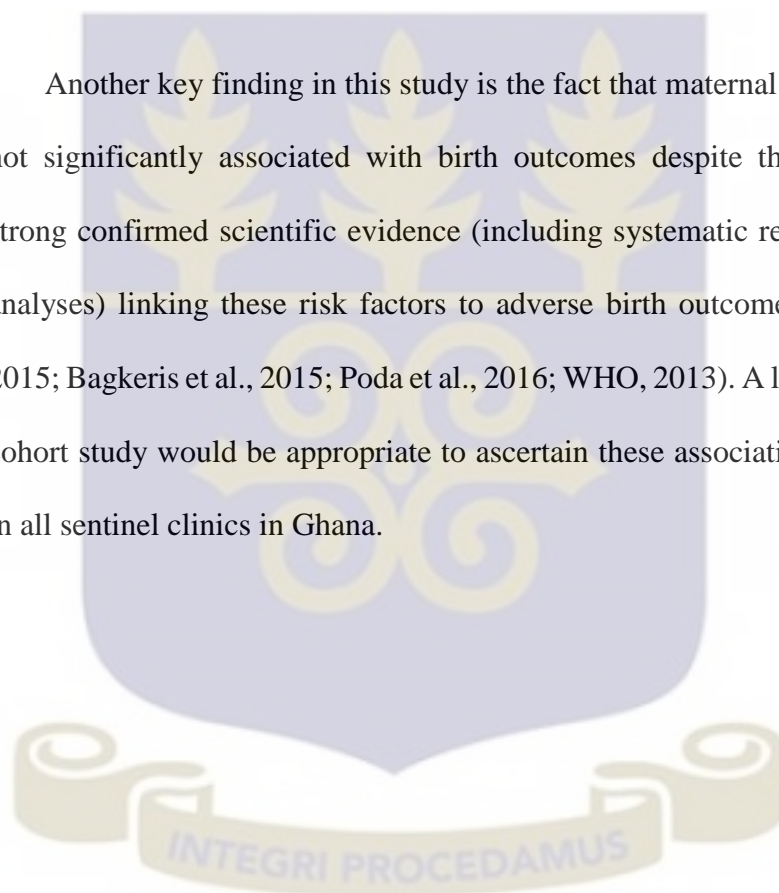
known mitochondrial toxicity, while stressing usage of fixed dose preferred regimens that have been proven to be less toxic (UNAIDS, 2013). While it may be understandable for the client who received dT4 in 2010, it is unfortunate that a client was still placed on dT4 in 2013.

This indicates the gravity of the situation when it comes to a lack of appropriate ARV supplies for the developing areas of the world. If appropriate regimens continue to be unavailable, there is no doubt that clinics will always do with whatever ARVs are available to them for use by clients. In fact, safety is a critical issue for pregnant women and their infants as well as women who might become pregnant. Thus, although data on ARV use in pregnant women remain limited, more data have become available since 2010 and provide increased reassurance for recommending TDF + 3TC (or FTC) + EFV as the first-line ARV regimen for pregnant women (Paredes et al., 2013).

Notwithstanding available scientific evidence pointing to an association between congenital defects and some ARVs, the study site did not record any such data and thus made it impossible for data to be obtained for congenital defects. One key congenital defect that has been recognized as been prevalent among ART recipient clients is neurogenital defects (Ford et al., 2014). Apart from good record keeping/consolidation, it is also very important to adhere to a comprehensive package of HIV prevention, diagnostic, treatment and support services provided for people living with HIV and their families. This is usually described as the continuum of HIV care. It includes initial HIV diagnosis and linkage to care; management of opportunistic infections and other comorbid conditions; initiating, maintaining and monitoring ART; switching to second-line and third-line ART; and palliative care (Paredes et al., 2013).

This study observes that the TTH follows these issues strictly but needs a more robust approach to deal with record keeping where the labor ward and other relevant units in the hospital can conveniently share and save data especially on a very vulnerable population as HIV clients. Efforts such as these would be of immense help to the research community and this will lead to producing or improving country specific guidelines in matters related to HIV/AIDS.

Another key finding in this study is the fact that maternal risk factors were not significantly associated with birth outcomes despite the availability of strong confirmed scientific evidence (including systematic reviews and meta-analyses) linking these risk factors to adverse birth outcomes (Alemu et al., 2015; Bagkeris et al., 2015; Poda et al., 2016; WHO, 2013). A larger prospective cohort study would be appropriate to ascertain these associations, if available, in all sentinel clinics in Ghana.



5.2 Conclusions

This Ghanaian retrospective cohort study was designed to determine the prevalence rates of HIV seropositivity, low birth weight, preterm deliveries and still births among a cohort of women who received ART at the Tamale Teaching Hospital from 2010 to 2015. The study also set out to ascertain whether these birth outcomes were associated with antiretroviral regimen used by the women. The results of the study provided prevalence rates of 4.2%, 18.8%, 7.3% and 5.0% for HIV seropositivity, low birth weight, preterm delivery and still birth respectively.

A large number of HIV infected women are put on alternative regimens instead of the preferred regimens due to a lack of supplies from key stakeholders. No associations were observed between birth outcomes and respective ARV regimens. Moreover, all the confounding maternal risk factors assessed in this study including smoking status, alcohol abuse, HIV type, etc were found to have no association with the observed birth outcomes. The WHO still has a long way to hit its target of ensuring that no newborns are infected with HIV by 2015.

5.3 Recommendations

Since more ART recipient women are willing to give birth, they must be supported through the established continuum of HIV care guidelines. In particular, robust strategies should be developed to significantly reduce the number of mothers who receive ART and end up delivering babies with the help of non-professional or traditional birth attendants thereby resulting in huge losses to follow-up of clients. The follow up of such pregnancies should involve a multidisciplinary range of health professionals collaborating for more favorable outcomes.

The Ghana Health Service should introduce requirements for sentinel clinics to record congenital defects resulting from ART. Policy makers need to establish systems that ensure that the most preferred ARV regimens are available for use while records/data are properly reconciled between different units at the hospitals to ensure that data is available for assessing important birth outcomes. Finally, there exist several critical evidence gaps that require priorities for future research in order to determine the complex relationships that exist between ART and birth outcomes. Governments and key stakeholders thus need to invest more into this area if the global goals of ending MTCT of HIV are to be achieved.

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APPENDICES

APPENDIX A: CHECKLIST FOR DATA COLLECTION

UNIVERSITY OF GHANA

SCHOOL OF PUBLIC HEALTH – DEPARTMENT OF EPIDEMIOLOGY AND DISEASE CONTROL

CHECKLIST SEEKING DATA ON: *“BIRTH OUTCOMES IN HIV POSITIVE WOMEN RECEIVING ART AT THE TAMALE TEACHING HOSPITAL.”*

	MATERNAL DEMOGRAPHICS					MATERNAL MEDICAL HISTORY						
<i>CLIENT ID</i>	<i>Age</i>	<i>Nationality</i>	<i>Religion</i>	<i>Educational level</i>	<i>Gravidity</i>	<i>Type of HIV</i>	<i>Specify ARV combination</i>	<i>Time of ART initiation</i>	<i>Specify any coinfections during ART</i>	<i>Mode of delivery</i>	<i>History of smoking</i>	<i>History of alcohol or other substance abuse</i>

	BIRTH OUTCOMES					CONGENITAL ANOMALIES AS PER MACDP GUIDELINES				
<i>CLIENT ID</i>	<i>HIV status</i>	<i>Birth weight</i>	<i>Preterm delivery</i>	<i>Still birth</i>	<i>APGAR score</i>	<i>Cardiovascular</i>	<i>Genitourinary</i>	<i>Musculoskeletal</i>	<i>Craniofacial</i>	<i>CNS</i>

LEGEND

ARV: Antiretroviral drug **ART:** Antiretroviral therapy **APGAR:** Appearance, Pulse, Grimace, Activity, Respiration **CNS:** Central Nervous System **HIV:** Human Immunodeficiency Virus **ID:** Identifiable Code **MACDP:** Metropolitan Atlanta Congenital Defects Program

APPENDIX B: ETHICAL CLEARANCE CERTIFICATE

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

*In case of reply the
number and date of this
Letter should be quoted.*

*My Ref. GHS/RDD/ERC/Admin/App
Your Ref. No.*



Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Tel: +233-302-681109
Fax + 233-302-685424
Email: Hannah.Frimpong@ghsmail.org

11th March, 2016

Amandus Ankobil
University of Ghana
School of Public Health
Legon, Accra

ETHICS APPROVAL - ID NO: GHS-ERC: 15/12/15

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol titled:

“Birth Outcomes in HIV Positive Women Receiving Antiretroviral Therapy at the Tamale Teaching Hospital: A Retrospective Study”

This approval requires that you submit yearly review of the protocol to the Committee and a final full review to the Ethics Review Committee (ERC) on completion of the study. The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Please note that any modification without ERC approval is rendered invalid.

You are also required to report all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.

You are requested to submit a final report on the study to assure the ERC that the project was implemented as per approved protocol. You are also to inform the ERC and your sponsor before any publication of the research findings.

Please note that this approval is given for a period of 12 months, beginning 11th March, 2016 to 10th March, 2017. However, you are required to request for renewal of your study if it lasts for more than 12 months.

Please always quote the protocol identification number in all future correspondence in relation to this approved protocol

SIGNED.....

PROFESSOR MOSES AIKINS
(GHS-ERC VICE-CHAIRPERSON)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra

APPENDIX C: SIGNED DATA SHARING AGREEMENT FORM

NATIONAL AIDS/STI CONTROL PROGRAMME (NACP)

*In case of reply the
number and date of this
letter should be quoted*

My Ref: nacp/gen/vol.15

Your Ref. No.



P. O. Box KB 547
Korle-Bu, Accra
Tel. (233-302) 67 84 57 - 9
Fax: (233-302) 66 26 91
Email: info@nacp.org.gh

11 May 2016

RE: SUPPORT OF DATA SHARING AGREEMENT: MR. AMANDUS ANKOBIL AND NACP

We wish to state that the National AIDS/STI Control Programme (NACP) has signed a data sharing contract with Mr. Amandus Ankobil of the Department of Epidemiology and Disease Control, School of Public Health, University of Ghana, to enable him acquire data for his research activities using HIV data at the Tamale Teaching Hospital.

In line with the above, please be informed that the NACP has agreed to allow Mr. Amandus Ankobil the right of limited access to the datasets for the research activities using HIV data at the Tamale Teaching Hospital.

He may therefore go ahead with the said research taking into consideration the conditions in the agreement.

We count on your cooperation.

**DR. STEPHEN AYISI ADDO
PROGRAMME MANAGER**

**THE CHIEF EXECUTIVE OFFICER
TAMALE TEACHING HOSPITAL
TAMALE**

cc: Mr. Amandus Ankobil
Dept. of Epidemiology and Disease Control
School of Public Health
University of Ghana
Legon – Accra

APPENDIX D: LETTER OF APPROVAL FROM TTH



Department of Research & Development Tamale Teaching Hospital

TTH/R&D/SR/16/184
03/05/2016

TO WHOM IT MAY CONCERN

CERTIFICATE OF AUTHORIZATION TO CONDUCT RESEARCH IN TAMALE TEACHING HOSPITAL

I hereby introduce to you **Mr. Amandus Ankobil**, an MSc Clinical Trials Student in the Department of Epidemiology and Disease Control of the School of Public Health, College of Health Sciences, University of Ghana, Legon. Who has been duly authorized to conduct a study on **"Birth Outcomes in HIV Positive women Receiving Anti-Retroviral Therapy at the Tamale Teaching Hospital: A Retrospective Study"**.

Please accord him the necessary assistance to be able to complete his study. If in doubt, kindly contact the Research Unit at the second floor of the administration block or on Telephone 0209281020. In addition, kindly report any misconduct of the Researcher to the Research Unit for necessary action, please.

Please note that this approval is given for a period of 3 months, beginning from 3rd of May, 2016 to 3rd of July, 2016.

Thank You.



ALHASSAN MOHAMMED SHAMUDEEN
(HEAD, RESEARCH & DEVELOPMENT)





