

ADHERENCE TO TREATMENT GUIDELINES FOR THE PREVENTION OF  
MOTHER-TO-CHILD HIV TRANSMISSION IN KENYA

By

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## **Abstract**

Access to the most effective treatments is not universal and treatment coverage for the prevention of mother-to-child transmission (PMTCT) is still low in many countries, including Kenya (WHO, 2010a). To improve uptake of PMTCT to reduce perinatal HIV transmission the World Health Organization (WHO) issued new treatment guidelines for use among pregnant HIV+ women in 2010 (WHO, 2010b). In the same year, Kenya's National AIDS and STI Control Programme (NASCOP) established revised guidelines for PMTCT. Despite expanded treatment guidelines it is unclear if women meeting the minimum requirements for treatment and ARV prophylaxis during pregnancy and postpartum follow-up are receiving treatment according to WHO and NASCOP recommendations. This study will examine the antenatal treatment regimens of HIV-infected women reporting to four hospitals in Kenya for Early Infant Diagnosis (EID) of HIV services. It will assess the extent to which PMTCT regimens of these HIV+ mothers reflect the revised PMTCT treatment guidelines, and if children born to mothers on less efficacious treatment regimes have higher HIV positivity rates.

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### **Abbreviations**

3TC	Epivir (brand name)/lamivudine (generic)
ABC	Ziagen (brand name)/abacavir (generic)
AIDS	acquired immunodeficiency syndrome
ANC	antenatal care
ARV	antiretroviral drug
ART	antiretroviral therapy
AZT	Retrovir (brand name)/zidovudine (generic); ZDV
CBO	community-based organization
EFV	Sustiva (brand name)/efavirenz (generic)
FTC	Emtriva (brand name)/emtricitabine (generic)
GHI	Global Health Innovations
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
KEMRI	Kenya Medical Research Institute
LPV/r	Kaletra (brand name)/lopinavir/ritonavir (generic)
MTCT	mother-to-child transmission
NACC	National AIDS Control Council
NASCOP	National AIDS and STI Control Programme
NFV	Viracept (brand name)/nelfinavir (generic)
NGO	non-governmental organization
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors



NVP	Viramune (brand name)/nevirapine (generic)
PI	protease inhibitors
PLWHA	persons living with HIV and AIDS
PMTCT	prevention of mother-to-child transmission
sd-NVP	single-dose nevirapine
STD	sexually transmitted diseases
STI	sexually transmitted infections
TDF	Viread (brand name)/tenofovir (generic)
UNAIDS	Joint United Nations Programme for HIV and AIDS
WHO	World Health Organization
ZDV	Retrovir (brand name)/zidovudine (generic); AZT

## CHAPTER 1

### Introduction

Globally, an estimated 34 million people are living with HIV/AIDS with 7,000 new infections occurring each day (UNAIDS, 2011a). Sub-Saharan Africa continues to be disproportionately affected by the virus as the region is comprised of 22.9 million individuals living with HIV. Roughly 16.8 million women and 3.4 million children are presently living with HIV worldwide (UNAIDS, 2011a). Kenya, with a total population of around 40.5 million (World Bank, 2010), has an estimated 1.6 million individuals living with HIV/AIDS (NACC, 2011). Kenya has the third largest population of individuals living with HIV/AIDS in sub-Saharan Africa. As of December 2011, around 6.2% of Kenyans between the ages of 15-49 are HIV-positive (NACC, 2011). HIV prevalence in Kenya peaked at around 10.5% in 1995-1996 (NACC, 2011). Women are disproportionately affected by HIV with 8% of adult Kenyan women infected compared to 4.3% of men. Approximately fifty-nine percent of all HIV infections in Kenya occur among women (NACC, 2011). As of 2009 there were 184,052 HIV-infected infants and children living in Kenya (NACC, 2010) with 12,894 new infections occurring among infants and children in 2011 (NACC, 2011) down 30% from 2010.

Increased financial and technical support from global health agencies and NGOs like the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis, and Malaria, have helped increase the proportion of eligible HIV+ people receiving ART from 7% in 2003 (WHO, 2006) to 47% in 2010 (UNAIDS, 2011b). Reducing the number of infants and children infected with HIV has been an imperative component of the global public health response to the HIV epidemic. Use of prophylactic ARVs during pregnancy dramatically reduces the risk of HIV-transmission to infants during pregnancy, labor and

delivery, or during breastfeeding from 15-45% (without ART) (WHO, 2012a) to as low as 1-2% (with ART, safe delivery, and replacement feeding) (Townsend et al., 2008). Thus, targeted prevention efforts among pregnant women in resource-poor settings are imperative to reduce HIV prevalence among future generations.

To establish global standards for HIV prevention and treatment, the World Health Organization (WHO) outlines treatment guidelines specific to the prevention of mother-to-child transmission (PMTCT) through antiretroviral therapy. Individual countries are encouraged to adapt WHO guidelines and release country-specific instructions based on their resources. In 2010 the WHO released an updated and more rigorous version of the PMTCT guidelines and Kenya's National AIDS and STI Control Programme (NASCOP) published National PMTCT guidelines shortly thereafter (outlined in sections 2.4 and 2.5).

However, access to the most effective treatments is not universal in Kenya. Despite expanded treatment guidelines, it is unclear if women meeting the minimum requirements for treatment and ARV prophylaxis during pregnancy and postpartum follow up receive treatment according to the revised global and national guidelines. Even in settings where ARVs are available, several clinical and patient-related barriers negatively impact the appropriate implementation of WHO and/or NASCOP PMTCT guidelines. Clinical barriers include inefficacious regimes and drug resistance, lack of service integration, weak healthcare infrastructure, and deficiencies in clinical training. Patient barriers include late or non-attendance at antenatal clinics, stigma, financial concerns, male and familial involvement, and loss to follow-up.

This study will examine the antenatal treatment regimens of HIV-infected women reporting to four government hospitals for Early Infant Diagnosis of HIV (EID) clinics in Kenya

from March 2010 to June 2012. The study aims to assess compliance with the 2010 revised PMTCT guidelines promoted by the WHO and NASCOP, and to assess if children born to mothers on less efficacious treatment regimes have higher HIV positivity rates.

## CHAPTER 2

### Review of Literature

#### **2.1. Seminal research in prevention of mother-to-child transmission (PMTCT) of HIV infection**

Antiretroviral therapy drug options were first proven effective in reducing mother-to-child HIV transmission in 1994 by the Pediatric AIDS Clinical Trials Group (PACTG 076) (Connor et al., 1994). An analyses by Connor and colleagues of 363 infants in the United States and France found that zidovudine (AZT) given during pregnancy and labor to mothers and postpartum to newborns, reduced MTCT at 18 months to 8.3% compared with a 25.5% transmission rate in the placebo group. However, the AZT regimen administered in the PACTG 076 trial was both complex and costly as antenatal dosing began at 14 weeks gestation. Following the results of the PACTG 076 trial it was evident that more cost effective ART would be necessary in order to reduce MTCT in resource-poor settings. Subsequent research (Shaffer et al, 1999; Dabis et al, 1999) attempted to decrease costs by providing later antenatal treatment initiation (i.e. 28 weeks or later) of AZT in mothers or in some cases eliminating postpartum ART prophylaxis in mothers or infants. Efficacy in successive research with AZT-only treatment was lower than that of the initial long-course PACTG076 (Connor et al., 1994, Lallemand et al., 2000), but still found to be better than rates among placebo groups (Dabis et al, 1999, Shaffer et al, 1999).

Previous research has demonstrated that earlier initiation of antiretroviral therapy during the antenatal period is more efficacious as is administration of ARVs during all three time frames of pregnancy (i.e. antenatal, intrapartum, and postpartum) (Lallemant et al., 2000, PETRA, 2002). PMTCT regimens with antenatal prophylaxis are preferred, however, many women do not present for PMTCT until delivery. As such, late course and postpartum regimens would also need to be considered. Lallemant and colleagues (2000) established that AZT prophylaxis started at 28 weeks gestation (1.6%) was more effective than prophylaxis started at 36 weeks gestation (5.1%) in preventing in-utero infections. However, many women do not present to the formal health sector until they are in labor. Accordingly, antiretroviral therapy administered only during the delivery and postpartum periods has also proven effective at reducing MTCT rates (PETRA, 2002), but treatment administered at delivery alone without postpartum therapy has not proven effective (PETRA, 2002).

Following PACTG 076 (Connor et al., 1994), several clinical trials successfully reduced MTCT rates utilizing shortened-course antenatal AZT regimes versus placebo (Dabis et al., 1999, Lallemant et al., 2000, Shaffer et al., 1999). In the early 2000's clinical trials began utilizing combination ART drug therapies, particularly regimen variations of nevirapine, zidovudine, and lamivudine, for use in PMTCT (Dabis et al., 2005, Lallemant et al., 2004, Moodley et al., 2003, PETRA, 2002). Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), became particularly popular for use in resource-constrained settings due to its low cost, quick absorption, and long-lasting biological half-life (i.e. the time it takes for half the drug to be eliminated from the bloodstream) (WHO, 2000). In 1999, preliminary results of the HIVNET 012 began to shift focus of PMTCT therapy to regimens consisting of single-dose nevirapine administered at delivery and postpartum (Guay et al., 1999, Jackson et al., 2003).

Rates of MTCT at 18 months among Ugandan infants in the HIVNET 012 trial were 15.7% among mothers receiving intrapartum sd-NVP and infants receiving sd-NVP after birth. MTCT was 25.8% among those receiving intrapartum AZT with 1 week of AZT follow-up for the infant. Results of the HIVNET 012 trial were controversial prior to the final results being published (Jackson et al., 2003, Jackson & Fleming, 2005, Swingle, 2001) due to concerns about alterations made in the trial methodology and study procedures. Ultimately the US Institute of Medicine found the HIVNET 012 results to be sound (Brierly, 2005) and thus sd-NVP became the regime of choice in the developing world. In 2000, Boehringer Ingelheim, the manufacturer of nevirapine began distributing free nevirapine to 59 developing countries making it both simple and affordable (Boehringer Ingelheim, 2007) and thus expanding PMTCT programs in the developing world.

Subsequent research found that single-dose nevirapine was more effective at reducing MTCT among breastfeeding infants in a South African clinical trial in which mothers were not administered prophylactic antiretroviral therapy. Breastfed infants receiving sd-NVP had a 12.2% transmission rate whereas infants given 6 weeks of AZT had a 19.6% MTCT rate ( $p = 0.03$ ) (Gray et al., 2005). This distinction was not observed among formula-fed infants. Another nevirapine trial with mothers and infants in Uganda, Ethiopia, and India (SWEN Study Team, 2008) compared MTCT rate after mothers received sd-NVP at delivery and infants received either sd-NVP at birth or NVP daily for 6 weeks post birth. Transmission rates were 5.3% in infants receiving only sd-NVP and 2.5% ( $p = 0.009$ ) in infants receiving extended nevirapine. At 6 month follow-up MTCT in infants receiving only sd-NVP was 9.0% and 6.9% ( $p = 0.16$ ) in infants receiving extended nevirapine. Moreover, infant mortality was significantly lower among the infants who received extended nevirapine (SWEN Study Team, 2008).

The SAINT trial (Moodley et al., 2003) observed comparable rates of MTCT at 8 weeks when comparing sd-NVP (12.3%) and combination therapy of AZT and 3TC (9.3%) administered at delivery and postpartum for both mother and infant. Research in Thailand (Lallemant et al., 2004) examined antenatal AZT along with either intrapartum AZT or sd-NVP and postpartum AZT with or without sd-NVP and found higher transmission rates among those that received AZT alone (6.3%) compared to AZT and sd-NVP (1.1%). MTCT transmission rates in participants receiving AZT and sd-NVP were similar to those found among infants in the United Kingdom and Ireland (Townsend et al., 2008). However, there was not a significant difference in MTCT rates among infants that received sd-NVP (2.0%) and those that did not (2.8%) (Lallemant et al., 2004).

Soon after PMTCT programs began to focus on sd-NVP, concerns began to arise about burgeoning resistance to nevirapine among HIV+ women and their infants. Due to nevirapine's long half life and low genetic barrier to resistance, most women and infants using sd-NVP will experience some resistance to the drug, if only temporarily (Arrivé et al., 2007, Cressey et al., 2005). Still, resistance is of paramount concern among women of child-bearing age as ARV resistance to short course prophylaxis regimens can reduce the efficacy of PMTCT and limit drug therapy options for future treatment or pregnancies. Viral resistance to nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), leads to resistance to other NNRTI drugs within the same drug class eliminating lower-cost options in the event of treatment failure. A meta-analysis conducted by Arrivé and colleagues (2007) found nevirapine resistance of 35.7% (n=950, CI: 23.0 – 50.6) among participants in 10 studies using single-dose NVP. Resistance of only 4.5% (n=223, CI: 2.1-9.4) was observed among 3 studies utilizing combination ARV therapy. Nevirapine resistance in infants was 52.6% (n=201, CI: 37.7 – 67.0) among infants in

seven studies with exposure to sd-NVP drug regimens compared with 16.5% (n=138, CI: 8.9 – 28.3) among infants in eight studies with exposure to combination ARV therapy (Arrivé et al., 2007).

Follow-up analysis of the Indian arm in the SWEN study (SWEN Study Team, 2008) also documented substantial rates of resistance among nevirapine exposed infants (Moorthy et al., 2009). Results of the resistance analysis revealed higher rates of drug-resistant nevirapine mutations among infants diagnosed with HIV in the first six weeks of life and randomized to the six-week extended nevirapine study arm (92%) versus the sd-NVP arm (38%) ( $p = 0.002$ ). This observation was also found among infants infected through breastfeeding and randomized to the six-week extended nevirapine arm (100%) versus the sd-NVP arm (27%) ( $p = 0.008$ ). Similarly, these alarming rates of resistance were also observed in an analysis of the Ugandan arm of the SWEN trial (Church et al., 2008).

While, sd-NVP is inexpensive and easy to administer, questions about increased risk of developing resistance encouraged WHO to remove sd-NVP from PMTCT treatment recommendations (WHO, 2010b). Triple antiretroviral prophylaxis or HAART options are now advised based on research indicating lower MTCT rates among women receiving triple ARV therapy for PMTCT (Kesho Boro Study Group, 2011, Kilewo et al., 2009, Shapiro, et al., 2010, Thomas et al., 2011). New research utilizing triple ARV therapy has also found reductions in MTCT rates, comparable to those in western countries (Townsend et al., 2008), even with later initiation of antenatal prophylaxis. Observational studies of women receiving antenatal and postpartum ZDV/3TC/NVP initiated at 34 weeks gestation found cumulative transmission rates of 5% at 6 months (Kilewo et al., 2009, Thomas et al., 2011). Randomized trials comparing triple antiretroviral therapies have had promising results. The Mma Bana study from Botswana



compared two triple ARV therapy options, both administered at 26 weeks through 6 months postpartum. Women received either ZDV/3TC/ABC or ZDV/3TC/LPV/r. For women receiving ZDV/3TC/ABC MTCT at 6 months was 2.1% and 0.4% among the ZDV/3TC/LPV/r arm ( $p = 0.53$ ) (Shapiro et al., 2010). The Kesho Bora study compared women receiving triple ARV therapy with ZDV/3TC/LPV/r to women receiving only dual therapy with ZDV + sdNVP beginning at 28 weeks gestation. Women in the triple ARV group also received postpartum therapy for 6 months whereas women in the dual therapy arm received ZDV/3TC for 1 week. Transmission rates at 12 months were 5.4% among the infants in the triple ARV arm compared to 9.5% in the dual therapy arm ( $p = 0.029$ ) (Kesho Boro Study Group, 2011).

## **2.2. Progression of antenatal care in Kenya: PMTCT, early infant diagnosis (EID), and infant feeding practices**

Pregnant women in Kenya generally have higher rates of uptake in prenatal services than women in comparable sub-Saharan African countries (World Bank, 2010). Kenya's PMTCT program, originally initiated on a pilot basis beginning in 2000, has expanded to integrate PMTCT services into existing maternal and child healthcare facilities. By the end of 2009, approximately 50% of Kenyan health facilities offered PMTCT services (NACC, 2010), and an estimated 58,591 HIV+ women received PMTCT treatment services that year (NASCO, 2011). In 2010, 37,204 HIV+ pregnant women in Kenya received antiretroviral therapy for preventing mother-to-child transmission. Approximately one-third of those enrolled in PMTCT receive an inadequate or inferior ARV regimen, and according to WHO, a projected 75 – 100,000 Kenyan women are in need of efficacious treatment (NACC, 2010, WHO, 2010a).

HIV testing, counseling, and referral services as well as access to antiretroviral therapy are the foundation of PMTCT. HIV testing and counseling should be provided as early as

possible in the pregnancy, so that women identified as positive can begin their PMTCT ARV regimen early enough to benefit themselves and their infant (WHO, 2007). The 2007 WHO recommendations (*Guidance on provider-initiated HIV testing and counseling in health facilities*) advise an opt-out approach to HIV testing, in an effort to routinize HIV testing among pregnant women and maximize the number of pregnant women screened. In 2010, 83% of pregnant women in Kenya were tested for HIV during their pregnancy (WHO, 2010a). Women that test negative should be re-tested again later in pregnancy and educated about how to avoid infection during the antenatal and postpartum periods.

Pregnant women identified as HIV+ are then encouraged to participate in the PMTCT program. PMTCT protocols that consider the woman's CD4 cell count (measure of her immune system strength), presence of any clinical symptoms, gestational stage, and treatment history inform the best ARV strategy PMTCT. Women with lower CD4 counts and those presenting at advanced gestational age need to start ART or ARV prophylaxis without delay during pregnancy, labor and delivery, and during the postpartum period to prevent MTCT.

Antiretroviral (ARV) prophylaxis is most successful at PMTCT when given during pregnancy, labor, and through the duration of breastfeeding; it can also be effective when started at the time of labor and when the infant is given ARV treatment after birth (WHO, 2010b).

HIV-infected mothers enrolled in PMTCT services are also counseled on infant follow-up care, including infant feeding practices. Formula replacement feeding is the only way to completely eradicate mother-to-child HIV transmission via breastfeeding. In resource-poor settings formula feeding isn't safe, affordable, feasible, or in many cases socially acceptable. Consequently, research has focused on determining the safest methods of breastfeeding for infants with HIV-infected mothers. Comparisons of exclusive breastfeeding and mixed-feeding

(e.g. combination of breastfeeding and formula feeding) have found lower rates of transmission among women who breastfeed exclusively (Ilf et al., 2005; Kuhn et al., 2007, Becquet et al., 2008). Kenya's PMTCT guidelines also outline best practices for infant feeding noting that replacement feeding is only advised when it is acceptable, feasible, affordable, sustainable, and safe for both mother and infant.

Early infant diagnosis (EID) was introduced in Kenya in 2006 as a subprogram of PMTCT with the aim of earlier detection and treatment initiation among HIV-infected infants. EID programs have grown rapidly from 434 health facilities serving 24,615 infants in 2007 to approximately 1,500 health facilities serving 55,604 infants in 2010 (NACC, 2011). As of 2009 approximately 61% of eligible children were tested for HIV (NACC, 2010). EID refers to diagnosing HIV in infants before 18 months of age and is extremely important due to rapid disease progression and a high mortality rate of HIV-infected infants. In the absence of intervention, one fourth of children with HIV die before their first birthday and the majority will die before age five. ARV treatment and co-trimoxazole prophylaxis have helped to substantially reduce infant mortality due to HIV infection. As of 2009, around 24.2% of eligible children and infants in Kenya are receiving HAART (NACC, 2010).

EID of HIV requires more expensive and sophisticated testing strategies. Because HIV antibodies are passed from mother to infant in utero and can persist in the infant for up to 18 months post-delivery (WHO, 2007), the HIV status of infants younger than 18 months cannot be determined with standard serologic or antibody tests. Rather, more costly virologic testing using HIV-DNA polymerase chain reaction (PCR) of dried blood spots is the gold standard for EID (WHO, 2010d), and has been identified as being structurally feasible in Kenya (Khamadi et al., 2008). Diagnosis of HIV in a child under 18 months is based on a positive HIV DNA PCR test,

ideally provided by 6 weeks of age. Infants can become infected with HIV during pregnancy, labor, or via breastfeeding during the postpartum period. Due to their undeveloped immune systems infants have quicker disease progression making the need for timely testing of paramount importance (Shearer et al., 1997, Rouet et al., 2003). Infections suspected during labor and delivery or postpartum will take longer to detect. In Kenya, EID guidelines indicate re-testing at 9 months and again at 18 months to rule out MTCT of HIV.

### **2.3. World Health Organization PMTCT Treatment Guidelines**

In 2001, the WHO published the first recommendations for ART treatment with nevirapine-based regimens in pregnant women (WHO, 2001). Revisions were made to the guidelines in 2003, 2006, and most recently in 2010. In addition to proposing earlier ART initiation for pregnant women, the changes suggest routine and accessible monitoring of CD4 cell count, an increased number of efficacious treatment options, and recommendations to discontinue use of drug regimes previously found to be less-tolerated among HIV-infected patients (WHO, 2010b, WHO, 2010c).

New global guidelines recommending earlier initiation and extended prophylaxis with HAART will significantly increase the number of individuals in need of adequate antiretroviral therapy. Stanecki and colleagues (2010) found that the number of individuals in low and middle income countries eligible for ART under the new guidelines would increase to 14.6 million under the 2010 guidelines compared to 10.1 million under the 2006 guidelines (Stanecki et al., 2010). Sub-Saharan Africa sees the majority of ART burden with an estimated 10.6 million individuals eligible for ART under the new guidelines compared to only 7.4 million under the previous ones. In Kenya alone, the new guidelines increase the numbers eligible for ART from 520,000 to around 750,000 individuals (Stanecki et al., 2010).

WHO guidelines specific to pregnant women and infants were also updated in 2010 based on evidence indicating that earlier initiation of HAART prophylaxis during pregnancy and extended postpartum treatment during the breastfeeding period could effectively reduce global MTCT risk to less than 5% (WHO, 2010b). Building upon the public health approach to PMTCT first introduced in the 2006 guidelines, the 2010 guidelines reiterate the importance of lifelong ART to pregnant women that meet treatment criterion. Additionally, the 2010 guidelines expanded the recommendations for treatment prophylaxis to include treatment both in early pregnancy and during breastfeeding rather than focusing strictly on the third trimester of pregnancy.

The new guidelines emphasize two treatment approaches for HIV-infected pregnant women: *lifelong ART* and *ARV prophylaxis*. Lifelong ART applies to HIV-infected women currently eligible for treatment on the basis of their own health as indicated by CD4 less than 350 or clinical symptoms. Pregnant women in need of lifelong HAART should be prescribed treatment regimes that are both safe and effective in PMTCT as the clinician should anticipate future pregnancies as well. ARV prophylaxis pertains to the temporary initiation of HAART during pregnancy, delivery, and breastfeeding when a pregnant woman is not in need of treatment based on her CD4 or clinical symptoms. Medications are administered until risk of MTCT is no longer present which is after the conclusion of breastfeeding post labor. Prophylaxis should be initiated as early 14 weeks of gestation or as soon as possible thereafter if the woman presents to care later in her pregnancy or during labor and delivery.

Under updated recommendations, women with a CD4 count of  $\leq 350$  cells/mm<sup>3</sup> should be started on ART regardless of clinical symptoms. Furthermore, women who present with advanced clinical symptoms as defined in WHO clinical stage 3 or 4 (Insert Figure 1 about here)

should start ART regardless of the CD4 count. For women who present in WHO clinical stage 1 or 2, CD4 testing is required to determine when to start ARV treatment or prophylaxis for PMTCT.

WHO (2010c) guidelines suggest two HAART treatment and prophylaxis options for HIV-infected pregnant women as found in Figure 2 (Insert Figure 2 about here). Option A includes twice daily AZT starting as early as 14 weeks gestation during the antepartum period, followed by single-dose NVP at commencement of labor, and concluded with AZT/3TC postpartum. Infants born to an HIV-infected mother receiving treatment via Option A should also receive daily NVP until after breastfeeding has ended. Option B includes triple ARV prophylaxis starting as early as 14 weeks gestation and continued until delivery or until 1 week after all infant exposure to breast milk has ended in the postpartum period. Similarly infants should receive daily NVP or twice daily AZT from birth until 4 to 6 weeks of age. In addition a WHO programmatic update released in April 2012 outlined Option B+ which suggests that triple ARVs be continued for life even among women started on prophylaxis regimes during pregnancy. WHO suggested this update in an effort to simplify regimes, reduce further sexual transmission of HIV, deter discontinuing and re-starting ARVs, and to offer further reduction of mother-to-child transmission if the mother becomes pregnant again.

#### **2.4. Kenyan Ministry of Health, National AIDS and STI Control Programme PMTCT Treatment Guidelines**

As of 2011, over half of women receiving PMTCT are treated under Option A (60%), however, the Kenyan Ministry of Health has agreed to begin transitioning to Option B+. By December 2012, the Ministry of Health plans to have 50% of pregnant women treated under Option B+ (Médecins Sans Frontières, 2012, Bachman and Phelps, 2012). Transitioning to

Option B+ would reduce the number of mother-to-child infections as lifelong ART would mean mothers would already be on treatment at the onset of future pregnancies. Kenya's commitment to update treatment guidelines to include Option B+ has been documented by global health organizations such as Médecins Sans Frontières/Doctors Without Borders, USAID and PEPFAR (2012). However, a programmatic update or addendum has not been issued by the Kenyan Ministry of Health.

The WHO (2009) suggests the adaptation of treatment guidelines based on six key principles to meet country-specific conditions as implementation of the guidelines may vary based on resources and disease burden. Guiding principles for adaptation: (1) maintaining current progress towards program objectives devoid of interrupting the care of individuals at highest risk, (2) seek to guarantee that clinically eligible individuals are able to enter treatment services, (3) maintain high standards for the quality of care, (4) make certain that access to treatment services is fair and just, (5) choose interventions which maximize public health impact with the most advantageous use of human and fiscal resources, and (6) recognize the enduring consequences and have a sustainability plan in place (WHO, 2009). In addition, countries are expected to adopt forward-looking interventions that strengthen health systems and take into consideration the perspectives of people living with HIV/AIDS. Countries are strongly encouraged to have phase-based plans in place that will eventually move the country towards full implementation of the guidelines. After the World Health Organization released updated treatment guidelines in 2010, Kenya's National AIDS and STI Control Programme followed suit releasing, *Guidelines For Prevention of Mother-Child Transmission of HIV/AIDS in Kenya* (Kenya Ministry of Health, 2010).

Drawing on the WHO guidelines, Kenya mirrored recommendations regarding when to start lifelong ART. However, recommendations for ARV PMTCT prophylaxis differed slightly from the WHO guidelines. Kenya's guidelines mirror WHO Option A. Women presenting for antenatal care are advised to start ARV therapy as early as 28 weeks gestation, compared to the WHO recommendation of 14 weeks gestation. Recommended regimens for WHO Option A and NASCOP are the same with AZT suggestion during the antepartum period, following by intrapartum sd-NVP and a seven day course of AZT/3TC administered postpartum. NASCOP does advise triple ARV prophylaxis, in accordance with WHO Option B, when feasible, a revision from the single-dose nevirapine regimes that were utilized under earlier guidelines. Recommended regimes for triple ARV prophylaxis also differed slightly between WHO and NASCOP recommendations.

Falling in line with WHO recommendations, NASCOP also updated clinical guidelines for PMTCT treatment initiation. NASCOP also recommends that women with a CD4 count of  $\leq 350$  cells/mm<sup>3</sup> should be started on ARVs regardless of clinical symptoms. In resource-limited areas where CD4 testing is not feasible, women can be started on ART in the presence of clinical symptoms at WHO stage 3 or 4 (Insert Figure 1 about here). When the CD4 count is  $>250$  and as resources allow, a protease inhibitor-based regimen utilizing lopinavir/ritonavir (LPV/r) is recommended over NRTI or NNRTI-based regimens. Administration of ARV prophylaxis varies and is dependent upon what stage of pregnancy the infected mother is in when she reports for antenatal visits.

## **2.5. Barriers, feasibility, and implications of PMTCT World Health Organization PMTCT Treatment Guidelines**



Although the latest treatment guidelines from both WHO and NASCOP expand the number of individuals currently in need of HIV treatment they do not necessarily provide easy paths to comprehensive implementation. Furthermore, barriers to antenatal care and uptake in PMTCT and EID programs make it difficult to implement appropriate access among all individuals currently in need of treatment. Research has identified clinical and patient-related barriers to uptake and implementation of PMTCT guidelines.

### **2.5.1. Clinical barriers**

*Inefficacious regimes and drug resistance* Single-dose nevirapine was long-considered the PMTCT drug of choice as it was safe, tolerable, and inexpensive. Research now shows poorer outcomes for mothers on sd-NVP regimes compared with those on triple-ARV therapy. A study conducted in Mombasa found that the MTCT at 14-16 weeks in a sample of 127 babies was 18.1%, similar to the transmission rate of 21.7% at 14 weeks post delivery and prior to the availability of NVP (Quaghebeur, et al., 2004). However, rates of transmission on sd-NVP regimes have varied. A study conducted in South Africa found a lower transmission rate of 9.9% among 294 mothers who receive sd-NVP administered between two and twenty-four hours prior to delivery and infants within 72 hours after birth (Colvin, et al., 2007).

Emerging resistance to NNRTI drugs, such as nevirapine, has been a primary concern in evolving treatment guidelines. According to Kenya's National AIDS Control Council, roughly 33% of HIV-infected pregnant women were treated with nevirapine only during antenatal care and follow-up as of 2009 (NACC, 2010). Research conducted by Delva and colleagues (2010) in Mombasa and the Kwale districts of Coast Province Kenya found that women in most Kenyan antenatal facilities were receiving an ARV regime of sd-NVP only (Delva et al. 2010).

Research conducted in Busia district of Kenya assessed the treatment regimes of 1668 pregnant women and categorized them according to their ARV regimen's adherence to the 2006 WHO guidelines (Azcoaga-Lorenzo et al., 2011). Regimes were separated into three categories: complete protocol, partial protocol, and no protocol. Based on these categories, the HIV status of the infants was examined after birth. From this sample, final HIV status post breastfeeding was obtained for 309 infants (HIV+, n=49; HIV-, n=260). Infants were 4.6 times more likely to be HIV+ if mother and infant received treatment according to partial protocols, and 43 times more likely to be HIV+ if mother and infant received no pharmaceutical intervention at all.

***Lack of service integration*** Numerous studies have included concerns about lack of service integration among the entire spectrum of family planning, antenatal care and follow-up. For example, studies have noted that many clinics often separate antenatal care and PMTCT. Some patients fear they will be seen in the waiting room with other patients that are known to be HIV-infected (Azcoaga-Lorenzo et al., 2011, Otieno, et al., 2010). Therefore, it would be advantageous to patients to provide PMTCT in the same clinical setting as antenatal care so that women are not publicly identified as being HIV-infected. On a similar note, more tightly integrating early infant diagnosis into antenatal care could strengthen infant testing, treatment, and uptake in EID.

***Weak healthcare infrastructure*** Research has demonstrated that Kenya has yet to fully implement prior versions of WHO and NASCOP guidelines even before the release of the 2010 guidelines (Azcoaga-Lorenzo et al., 2011, Delva, et al., 2010). In order for proper implementation of the newest treatment guidelines clinicians must have access to all of the recommended resources. The newest version of the guidelines relies heavily on the availability of CD4 cell count assessment which has limited availability in many clinical settings (Azcoaga-

Lorenzo et al., 2011). In addition, health care facilities are frequently short staffed and health care workers are overburdened. As a result, many patients experience long wait times when trying to access antenatal care (Anand et al., 2009, Bwirire et al., 2008). These issues have led some patients to report a lack of faith in their health care services (Otieno et al., 2010) which contributes to lack of continued care.

***Deficiencies in clinical training*** Kenya currently has only 0.1 physicians for every 1,000 inhabitants compared to 7.9 physicians for every 1,000 inhabitants in European countries (World Bank, 2010). Kenya, like many countries in the developing world has experienced medical “brain drain,” with many Kenyan-trained physicians leaving to practice medicine in Western countries. Physicians and medical personnel often report feeling overburdened, overworked, and ill-prepared in light of Kenya’s health situation (NACC, 2011). Inadequate training of service providers and lack of understanding of PMTCT and EID referrals has created difficulty in some patients reporting for care (Hassan et al., 2012).

As a result of training deficits, patients have also encountered problems with clinical staff bias in regards to their chosen feeding practices for infants. Women have reported that overly enthusiastic clinical staff can be pushy in encouraging patients to partake in artificial feeding even though the social environment is not conducive to artificial feeding. Bottle-feeding is not feasible for most women as it is both expensive and would disclose their status to others (Bwirire, et al., 2008). Moreover, HIV testing procedures for mothers reporting for antenatal care have also been a source of losing patients to follow up. Opt-out testing is recommended by WHO (2007) due to higher test acceptance and the ability to identify more infections. While opt-out testing provides patients with the option to decline testing, some patients report feeling forced to consent to HIV testing (Bwirire et al., 2008, Ujiji et al., 2011). Patients have admitted to test

acceptance due to pressure from overzealous staff. Others have cited pressure to consent for testing due to worries that testing was somehow connected to their ability to access antenatal care services in the future.

### **2.5.2 Patient-related barriers**

*Late or no antenatal clinic attendance* Patients engaging in HIV care prior to developing the clinical symptoms of HIV disease experience better health outcomes. Likewise, HIV-infected pregnant women reporting for antenatal care and PMTCT treatment earlier and more often in pregnancy will also have the best health outcomes. Currently, the 2010 NASCOP PMTCT guidelines recommend women complete a minimum of four antenatal clinic visits. According to NASCOP guidelines ARV prophylaxis should be initiated from 28 weeks gestation or as soon as possible thereafter. WHO guidelines suggest treatment initiation as early as 14 weeks gestation.

Using data collected from 25,364 pregnant women at antenatal clinics in Coast Province, Kenya, Delva and colleagues (2010) found that only 13.6% of urban women and 8.8% of rural women attended four or more antenatal visits. Furthermore, 52.2% of rural women and 49.2% of urban women attended antenatal clinic visits only once, and 30% of all women in the study had their first ANC visit after 28 weeks gestation. Even with extensive community-based involvement with active participation in the promotion of ANC services, in one study only 10% of women completed the four-visit schedule (Delva, et al., 2010). Evidence suggests that initiating ART PMTCT prophylaxis starting on the very first ANC visit could motivate patients to engage in care and follow-up in care.

Another factor contributing to lackluster antenatal clinic care attendance is home delivery. The National AIDS Control Council of Kenya reports that as of 2009 only 44 percent

of pregnant women give birth at a health facility. Mothers who deliver at home are also more likely to have poorer adherence to ARV treatment (Azcoaga-Lorenzo et al., 2011).

**Stigma** Stigma, denial, and fear of societal rejection continue to be some of the greatest barriers to accessing care for many HIV+ individuals. Surveys conducted among 116 Kenyan women post PMTCT care found that stigma was cited by over 78% of participants as a barrier to accessing care (Otieno et al., 2010). Stigma is often the key barrier in disclosure of HIV status to family and friends (Azcoaga-Lorenzo et al., 2011, Kulzer et al., 2012). Involving religious leaders, healers, and other individuals with obvious influence on the community in HIV outreach and education is one way to reduce this stigma (Bwirire, et al., 2008).

**Patient financial concerns** Kenya's HIV prevalence is highest among the top wealth quintile (7.2%) and lowest among Kenya's lowest wealth quintile (4.6%) (NACC, 2011). User fees for ANC services were removed in 2007. However, many women still face financial and transportation issues which regularly hinder timely and consistent presentation to ANC visits and EID follow up (Bwirire et al, 2008, Delva et al., 2010, Hassan et al., 2012, Otieno et al., 2010). Women in rural areas, in particular, report struggling with transportation issues as a result of having to travel to a more central or urbanized setting to access clinical services.

**Male and familial involvement** Several studies mention lack of familial involvement, particularly that of the father of the baby as a barrier to uptake in PMTCT and ANC follow up (Bwirire et al., 2008, Delva et al., 2010, Kulzer et al., 2012, Otieno, et al., 2010). Male partners wield significant influence in regards to their female partner's infant feeding choices and adherence to PMTCT-prescribed antiretrovirals (Otieno et al., 2010). Yet it is uncommon for men to be present with mothers during antenatal visits and delivery. As such there is a missed opportunity to offer HIV testing to both partners. Furthermore, engaging entire familial units in

care can help to combat stigma and promote understanding. A study conducted in the Nyanza province of Kenya (Kulzer et al., 2012) utilized a family model of care to link HIV+ index patients to their other family members at risk. The family model of care is used to identify and offer care to all of a patient's HIV-infected family members as well as present education that will prevent new infections among family members that are not HIV-infected. Among 285 HIV+ index patients there were 725 (2.5 per index patient) family members identified as at risk for HIV. Of the 725 at-risk patients, 62% (n=452; 1.6 per index patient) were tested for HIV and 39% (n=175) were found to be HIV+.

Disclosure, particularly to male partners, for many women can be serious and sometimes even violent (Bwirire et al., 2008, Kulzer et al., 2012, Otieno et al., 2010). However, disclosure is crucial and can facilitate the partner's awareness about their need to test. Women who voluntarily choose not to access HIV care are more likely to report having a male partner that has a negative attitude to HIV care or is not aware of their diagnosis. Consequently clinics are beginning to integrate clinical staff that can counsel patients in regards to disclosure (Kulzer et al., 2012). In addition, clinics are being encouraged to adopt a more family oriented approach to care which will ultimately results in reducing familial stigma and increasing HIV testing among partners and families.

***Lost to follow up*** Maintaining high retention rates in PMTCT is the only way to ensure prevention of mother-to-child transmission is taking place. Maternal factors (e.g. younger maternal age, lower education attainment, location, etc.) have been associated with failure to follow-up with PMTCT and EID care (Azcoaga-Lorenzo et al., 2011, Hassan et al., 2012, Otieno et al., 2010). Older women have been found to have their first antenatal visit earlier and follow

up more frequently during pregnancy than younger mothers (Delva et al., 2010). Rural women were also more likely to report for antenatal care earlier in their pregnancy.

Some mothers express discomfort that PMTCT is too infant-focused and express dissatisfaction that not enough emphasis is put on the mother herself. Of particular concern was unavailability of ART when a mother believed herself to be ill enough to be offered PMTCT with ART (Bwirire, et al., 2008, Otieno, et al., 2010). Mothers are only offered ART according to guidelines and medication availability and do not recognize the necessity of follow up if they are not immediately eligible for ART. Only half of women referred for long-term treatment and care post PMTCT actually follow up (Otieno et al., 2010).

## **2.6. Purpose of the study**

This study will examine the antenatal treatment regimens and mother-to-child transmission rates of HIV-infected mother and infant pairs receiving early infant diagnosis services at four government hospitals in Kenya.

The study aims to: (1) describe antenatal treatment regimens documented for each mother to determine (a) the proportion of mothers who meet the 2010 World Health Organization (Options A and B) and Kenyan National AIDS and STI Control Programme Guidelines for the Prevention of Mother to Child Transmission (PMTCT) of HIV/AIDS in Kenya, (b) explore what PMTCT treatment regimens were followed at four hospital study sites, and (c) determine the trend in adherence to national and global guidelines from 2010 to 2012.

Also the study aims to (2) assess if the infants born to mothers receiving no or insufficient PMTCT care were more likely to be diagnosed HIV positive.

## **2.7. Study Hypotheses:**

Hypothesis 1: More mothers will be treated in accordance with NASCOP guidelines than WHO guidelines at the four hospital sites because NASCOP guidelines are more lenient. Among hospital sites that adhere to WHO guidelines, more mothers will be treated in accordance with WHO Option A than Option B for the same reason as WHO Option A is more lenient than WHO Option B.

Hypothesis 2: There will be a trend towards improved adherence to both WHO and NASCOP guidelines from 2010 to 2012 as the guidelines are becoming widely disseminated.

Hypothesis 3: Infants born to mothers who received no or insufficient PMTCT regimens will have higher rates of HIV-infection.

## Chapter 3

### Methodology

#### 3.1. Background

Beginning in 2011, Global Health Innovations (GHI) and the Kenya Medical Research Institute (KEMRI) began piloting the HIV Infant Tracking System (HITSsystem©) intervention in Pumwani Maternity Hospital in urban Nairobi, and shortly thereafter expanded to Mathare Hospital in Nairobi as well the Kapsabet and Kericho District Hospitals in the rural or peri-urban regions of western Kenya. A map depicting the hospital locations is presented in Figure 3 (Insert Figure 3 about here).

A pre-post intervention evaluation design was employed to assess the impact of the HITSsystem© on key EID outcomes. The HITSsystem© is an online system that captures relevant data for the mother and infant at enrollment and subsequent visits, utilizing an algorithm programmed by the infant's date of birth to generate automated action alerts when time-sensitive interventions for testing or treatment have been missed. Mothers' PMTCT regimen, infant testing



information, and HIV status were among the additional variables collected through the HITSystem©.

For the purposes of this study, a secondary analysis was conducted to determine if maternal and infant drug regimes were administered according to WHO and NASCOP guidelines. Dr. Sarah Finocchiaro-Kessler, Assistant Professor at the University of Kansas Medical Center and a collaborator with Global Health Innovations, provided the de-identified data for this thesis. The EID registries used prior to the HITSystem© indicated if the mother had PMTCT, but data regarding regimen and week of initiation were incomplete. Data collected through the HITSystem© intervention captured more comprehensive PMTCT-related data, and thus this analysis only utilized data collected through the HITSystem© (start date in April 2011). In addition an analysis was conducted to assess if infants born to mothers on less efficacious treatment regimes were more likely to test positive for HIV.

### **3.2. Sample**

De-identified data for a total of 853 mother-infant pairs enrolled in early infant diagnosis (EID) were collected by clinical staff at each of the four hospitals using the HITSystem©. Pumwani Maternity Hospital and Mathare District Hospital are located in urban Nairobi. Kapsabet and Kericho District Hospitals are located in rural areas of western Kenya. All mothers presenting with their infants for EID follow-up were HIV+. Contextual information provided by clinical and research staff found that nearly all participants receiving care at these government hospitals are black Kenyans. Immigrants from neighboring African countries residing in Kenya may also be included in the patient population.

### **3.3. Procedures**

As per the existing protocol at each of the hospitals, data regarding mothers' PMTCT history were collected both verbally from mothers at the time of enrolling their infant in EID care, and were cross referenced with the mother's medical file.

Maternal and infant data were collected through the HITSystem© for the duration of infant's enrollment in EID care. Mothers' were informed about the HITSystem© and given the opportunity to decline participation, in which their information was collected in the EID registry notebook (standard of care). No mothers opted to decline participation with the HITSystem©. Clinicians and staff at each facility were trained by Global Health Innovations staff on electronic reporting via the HITSystem© and informed consent procedures.

The study protocol was approved by Institutional Review Board at the Kenya Medical Research Institute (KEMRI). Approval for this project was not sought through the University of Kansas Human Subjects in Research Committee. De-identified data were accessed from Global Health Innovations and analyzed for educational purposes only. The data analyses and written report are for the purposes of partial completion of a Master's thesis, a required component of the Global and International Studies program at the University of Kansas. The findings of this study will not be used for generalization purposes and the student-researcher has no intention of publishing or disseminating the findings presented in this master's thesis.

### **3.4. Data cleaning and management**

Data related to relevant variables were imported into excel files from the HITSystem© for each hospital, and were cleaned and coded in separate excel files before being merged into SPSS for analysis. Due to the nature of data collection there were instances where the mother's medical file indicated that they received PMTCT prophylaxis, but the regimen was marked as "unknown" (N=15) or "other" (N=85) in the HITSystem©. As a result, these incomplete cases

were left out of the analyses when establishing whether a mother-infant pair meets the treatment guidelines as it is impossible to determine based on the available data. All statistical analyses were performed using IBM SPSS© version 20 for Windows.

### **3.5. Variables**

To address hypothesis 1, regarding the percentage of mothers treated in accordance with NASCOP and WHO guidelines, PMTCT drug regimens and week of PMTCT treatment initiation were examined for each mother included in the sample. Drawing from the study model of Azcoaga-Lorenzo and colleagues (2011) regimens were coded into four categories: (1) meets guidelines (ARV prescribed in perfect agreement with guidelines), (2) late treatment initiation (correct ARVs prescribed later than guidelines recommends), (3) insufficient treatment (incorrect ARV regimen), or (4) no intervention (no ARV prescribed). As stated above, cases where mothers' PMTCT regimen could not be determined were left out of the analysis. The grouping variable categorizing mother-infant pairs by hospital served as the independent variable and the variables examining whether or not each mother received PMTCT according to the guidelines was the dependent variable.

Three new variables were created to indicate if the mother was treated in compliance with NASCOP, WHO Option A, and WHO Option B guidelines. If mothers were treated with AZT, dual AZT therapy, or HAART and treatment initiation was 28 weeks or sooner they were coded as '1' for meeting NASCOP guidelines. If mothers were treated with AZT, dual AZT therapy, or HAART and treatment initiation was 14 weeks or sooner they were coded as '1' for meeting WHO Option A guidelines. If mothers were on HAART therapy they were coded as '1' for meeting WHO Option B guidelines.

Hypothesis 2 addresses week of treatment initiation to assess if there has been a trend towards earlier treatment initiation from 2010 until 2012. Mother-infant pairs were coded into categories based on their date of birth and an assumed 40 week gestation period. Given that WHO recommends PMTCT beginning shortly after the second trimester, infants were coded based on the year in which the majority of the final two-thirds of gestation occurred (i.e. 1=2010, 2=2011, and 3=2012). The grouping variable examining year of pregnancy served as the independent variable and week of treatment initiation was the dependent variable.

PMTCT regimens and infant HIV status were examined to address hypothesis 3. Infants were coded as '0' if HIV-negative, '1' if HIV-positive, and '2' if HIV test results were indeterminate. Mothers were coded as '1' if they were on PMTCT that included AZT alone or dual AZT therapy, '2' if they were HAART, and '3' if they were on NVP. Mothers that were on regimens marked as "unknown" or "other" were left out of this analysis. Infant HIV status was the dependent variable in this analysis and mother's PMTCT treatment regimen was the independent variable.

### **3.6. Analyses**

To describe the quality of PMTCT services at the four study hospitals, various statistical analyses were conducted. Frequencies and percentages were calculated for categorical variables such as whether mothers received PMTCT therapy, PMTCT regimens, and infant HIV status. Measures of central tendency and variability (mean, median, range, and standard deviation) were examined for continuous variables such as week of PMTCT treatment initiation.

To address hypothesis 1 and determine if WHO and NASCOP-specific PMTCT guidelines were met, two criteria were evaluated: regimen and week of treatment initiation. To address the second hypothesis, ANOVA was used to compare week of treatment initiation

between mothers receiving PMTCT in 2010, 2011 and 2012. To answer hypothesis 3, frequencies and percentages were examined to determine if infant's HIV status was associated with the absence of PMTCT care of the mother.

## CHAPTER 4

### Results

#### 4.1. Describing PMTCT care among HIV+ women

Among the 853 mother-infant pairs, 85.11% (n=726) received some form of antiretroviral therapy for the prevention of mother-to-child HIV transmission. Average week of PMTCT treatment initiation among mothers was 24.02 weeks with a median and mode of 28 weeks, and standard deviation of 9.80 weeks. Week of treatment initiation at individual hospitals will be described in greater detail in section 4.2.

Pumwani Maternity Hospital experienced the highest percentage of women receiving PMTCT with 97.63% of mothers receiving treatment. Mathare District Hospital, similar to Pumwani, also had a high proportion of mothers on PMTCT with 90.32% of mothers receiving treatment. Kapsabet and Kericho District Hospitals had the lowest percentages of mothers receiving PMTCT with 64.23% and 56.69% respectively.

As stated earlier, PMTCT regimen information was marked as “other” in 85 cases and “unknown” in 15 cases. As a consequence, only 86.23% (n= 626 out of the 726 mothers who received PMTCT) mother-infant pairs were analyzed for PMTCT regimen-specific data. Of the 626 mothers where PMTCT regimen is documented the most common regimen among all four hospitals was AZT alone or in combination with either NVP or 3TC (n=598, 95.5%). HAART was the second most common regimen (n=23, 3.7%), and 5 (0.01%) mothers reported being

treated with nevirapine only. Table 1 depicts a breakdown of the sample and overall findings by hospital (Insert Table 1 about here).

#### **4.2. Meeting national and global PMTCT guidelines**

Table 2 shows the proportion of mothers that received PMTCT in accordance with each of the treatment guidelines (i.e. NASCOP, WHO Option A, and WHO Option B). Table 3 shows the same proportions, but also includes a breakdown of mothers that were treated with insufficient regimens, receiving late treatment initiation, or no treatment intervention. The majority of mothers were treated in accordance with NASCOP guidelines (n=577, 76.6%) which in this case meant they were treated with an ARV regime that included AZT or HAART commencing at 28 weeks gestation. WHO Option A requires AZT or HAART commencing at 14 weeks gestation. Only 63 (8.4%) mothers met the treatment requirements for WHO Option A. Requirements for WHO Option B recommend HAART commencing at 14 weeks gestation. Only 13 (1.5%) mothers met the recommendations for WHO Option B. Hypothesis 1 was validated as the majority of mothers were treated under the NASCOP guidelines followed by WHO Option A and then WHO Option B.

In total 44 (5.8%) mothers received late treatment initiation according to NASCOP guidelines (i.e. treatment initiation later than 28 weeks gestation). This number increased substantially when looking at WHO Option A with 558 (74.1%) of mothers receiving late treatment initiation under Option A. Of the 23 mothers receiving the triple antiretroviral therapy or HAART regime required under WHO Option B, 10 (1.3%) received late treatment initiation according to WHO Option B.

Pumwani had the highest overall proportion of mothers treated in accordance with NASCOP guidelines as 96.7% (n = 436) were treated. Mathare had the second highest with

72.4% (n = 63), followed by Kapsabet with 41.8% (n = 46), and Kericho with 30.5% (n = 32).

When looking at WHO Option A, Mathare had the highest overall proportion of mothers treated in accordance with guidelines with 39.1% (n = 34) of mothers treated according to Option A.

Kericho had the second highest proportion treated in accordance with Option A at 13.3% (n = 14), followed by Kapsabet with 11.8% (n = 13), and Pumwani with 0.4% (n = 2). All 13 of the infants treated in proper accordance with WHO Option B were at the Kapsabet District Hospital.

### **4.3. Trends in PMTCT care**

A one-way ANOVA (Insert Table 4 about here) was conducted to determine if earlier PMTCT treatment initiation was observed from the time updated treatment guidelines were released in 2010 until 2012. Mean week of treatment initiation was calculated for each year and are presented in Table 4 as well as Figure 4 (Insert Table 4 and Figure 4 about here). There was a significant change or improvement in week of PMTCT treatment initiation observed at the  $p < .05$  level over the three years [ $F(2, 723) = 13.725, p = 0.000$ ]. Post hoc comparisons using the Tukey HSD test (Insert Table 5 about here) indicated that the mean week of treatment initiation in 2010 ( $M = 27.11, SD = 5.24$ ) was significantly different than both 2011 ( $M = 23.19, SD = 10.61$ ) and 2012 ( $M = 20.26, SD = 11.77$ ). There was no significant difference between week of treatment initiation in 2011 and 2012. However, it is important to broach the 2012 findings with caution as there as a low number of mother-infant pairs in the 2012 category ( $N = 34$ ) compared with 2010 ( $N = 180$ ) and 2011 ( $N = 512$ ). Standard deviation and standard error was high in the 2012 category ( $SD = 11.77$  and  $SE = 2.019$ ). Nevertheless, the significant difference between 2010 and 2011 suggest that Kenya is moving towards greater adherence to WHO Option A guidelines and also validates hypothesis 2.

Mean week of treatment initiation varied between hospitals (Insert Figure 5 about here). Mathare had the earliest mean week of treatment initiation at 14.08 weeks gestation followed by Kapsabet with 16.68, Kericho with 24.00 weeks, and Pumwani with 27.90 weeks.

#### **4.4. HIV transmission among infants**

Among the infants participating in EID care, 95.55% (n=815) were tested for HIV. Among the 815 infants that were tested for HIV, forty-one infants were found to be HIV positive and 3 had indeterminate HIV results. Overall HIV prevalence among infants tested in the sample was 5.03%. HIV prevalence varied between hospitals. Pumwani Maternity Hospital had the lowest infant HIV prevalence at 2.37% followed by Kericho District Hospital with 2.75%. Kapsabet and Mathare District Hospitals had the highest infant HIV prevalence in this sample. At Kapsabet 8.96% of infants were HIV-infected and at Mathare HIV prevalence was the highest of the four hospitals at 13.89%. Of the 41 positive infants, mother's PMTCT status and regimen was known for 35 of the positive infants. The remaining 6 were mothers on PMTCT regimens marked as "unknown" or "other."

Hypothesis 3 was validated in examining treatment regimens. Of the 35 HIV+ infants where mother's PMTCT regimen was known, 16 received no PMTCT intervention comprising 14.03% of the total sample of untreated mothers. Nineteen of the HIV+ infants had mothers who received a single or dual combination AZT regimen comprising 2.72% of total sample of mothers receiving PMTCT. None of the infants receiving triple antiretroviral therapy or nevirapine-only regimens tested positive for HIV. As stated earlier, 6 of the infants who tested HIV+ had mothers who were on PMTCT regimens marked as "unknown" or "other."

## **CHAPTER 5**

### **Discussion**



### 5.1. Strengths and limitations

Reported uptake in PMTCT therapy was high among this sample with 85.11% of mothers receiving PMTCT. Kenya's National AIDS Control Council (2011) reported that 69.2% of women received PMTCT in 2011. One of the best successes to report in in this sample was the minimal use of single-dose nevirapine as PMTCT therapy. Only 5 (0.01%) women on PMTCT prophylaxis in this sample were treated with single-dose nevirapine compared to the 2011 Kenyan national average of 4.2% (NACC, 2011). Both the national average and the average found amongst the sample in this study are a success for the rapid dissemination and implementation of the NASCOP and WHO guidelines.

Future research is planned to examine the success of the HITSys<sup>TM</sup> intervention focusing on EID indicators both pre and post HITSys<sup>TM</sup>. HIV prevalence among infants in this sample was similar to national averages at 5.03%. However, prevalence varied between hospitals and Mathare District Hospital experienced a much higher infant HIV prevalence at 13.89% than the other hospitals. This is troublesome given the fact that uptake in PMTCT was high with 90.32% of women at Mathare receiving PMTCT therapy. In addition, Mathare also had the earliest week of treatment initiation at 14.08 weeks and the highest proportion of mothers treated in accordance with WHO Option A as opposed to the less stringent NASCOP guidelines. Given this information, one would expect Mathare to have the lowest proportion of HIV+ infants. However, the Mathare district is one of Kenya's largest slums (Karanja and Makau, 2010) and quality of life and health indicators could also be impacted by larger biological and socioeconomic factors. Further exploration into Mathare's outcomes may be necessary and could be identified if additional social and economic demographic variables were collected in the future.

Pumwani had the best outcomes overall with the highest percentage of mothers treated in accordance to NASCOP guidelines and the lowest percentage of HIV+ infants. This could be due in part to the specialized nature of Pumwani as the only hospital in the sample focusing strictly on maternal and child health. By incorporating PMTCT and EID care into the normal flow of maternal health services perhaps Pumwani is able to better manage and follow up with patients. Pumwani's positive outcomes could be attributed to their integration of PMTCT services into their antenatal care program which was discussed as a potential barrier earlier in this thesis (Azcoaga-Lorenzo et al., 2011, Otieno, et al., 2010). Based on their strict adherence to the NASCOP guidelines and high uptake in both PMTCT and EID services it would be worth taking a closer look at their services and clinic flow to determine if it would be an appropriate model for other clinics in Kenya.

There are several additional limitations in this study. Data regarding mother's PMTCT regimen were limited in 100 cases and variables in some cases were missing entirely. The reality of collecting global health data in the field warrants discussion as it is important to point out that data were collected from currently-operating EID programs. The HITSystem© is a resource designed for utilization in a clinical setting and is dependent upon self-reported PMTCT history as well as human data entry and chart review. As a result, missing information regarding PMTCT regimens were regarded as untreated when in reality the information may not have been available or obtained. The high number of PMTCT regimens entered at "other" or "unknown" (n = 100) was also problematic in this sample. These individuals had to be left out of analyses examining PMTCT regimens and 6 of the 41 infants that were HIV+ had mothers on PMTCT regimens marked as "other" or "unknown." It would be particularly helpful to obtain the mother's PMTCT regimen in cases where the infant had an indeterminate or HIV-positive test

result. The 100 “missing” or “unknown” regimen cases were dispersed evenly across all of the hospitals so perhaps follow up with each site to determine why regimens were entered into the HITSsystem© this way would be advantageous.

Second, additional variables such as mother’s age, education level, socioeconomic status, or substance use could more thoroughly explain the outcome of these findings, but were not collected. Moreover, the data included self-reported PMTCT regimen history; however there was no variable that could be used to measure or predict adherence to antiretroviral therapy. Consequently, it cannot be determined if PMTCT medications were taken consistently, correctly, or at all. Previous research (Azcoaga-Lorenzo et al., 2011, Delva et al., 2010, Hassan et al., 2012, Otieno et al., 2010) has demonstrated that demographic characteristics such as mother’s age, education level, socioeconomic status, or substance use can also influence adherence so in the future it would be helpful to have comprehensive demographic information about mothers. Further, previous research has demonstrated that mothers who deliver at home also report lower adherence to PMTCT therapy (Azcoaga-Lorenzo et al., 2011, NACC, 2011). Such mothers need to be brought into mainstream care to prevent mother-to-child transmission of HIV.

Third, governmental and societal factors could have also impacted the results of this study. Overall findings of this study with low nevirapine use, high percentages of mothers receiving PMTCT, and a movement towards earlier week of treatment initiation indicate a rapid uptake in the new NASCOP and WHO guidelines. Despite the fact that there are guidelines in place it can often take several years to disseminate guidelines for full implementation by providers and some bottlenecks or treatment gaps will continue to persist. With the HITSsystem© intervention in place it will be possible to examine regimen data again in the future and include a more exhaustive sample over a longer period of time. Furthermore, it will be valuable to examine

future regimen data to see if greater movement is seen towards adherence to Options B/B+ as the Kenyan government is committed to establishing Options B/B+ as the standard of PMTCT care in upcoming years (Médecins Sans Frontières/Doctors Without Borders, 2012, Bachman and Phelps, 2012).

Fourth, one major clinical outcome missing from this sample was the mother's CD4 and viral load during pregnancy. Collecting the mother's clinical measures for CD4 and viral load may also be a helpful indicator as women with lower CD4 and higher viral load are more likely to transmit HIV infection to their infants (Cole et al., 1997, Rousseau et al., 2003). This information could be useful in explaining the cases where infants tested positive in spite of having mothers on adequate treatment.

## **5.2. Implications for research, policy, and practice**

Both NASCOP and WHO Option A recommend AZT during the antenatal period for PMTCT. The key difference between the guidelines for NASCOP and WHO Option A is week of treatment initiation. NASCOP guidelines recommend commencing treatment at 28 weeks gestation or as soon as possible thereafter, whereas WHO Option A recommends 14 weeks. From 2010 to 2012 a positive and statistically significant trend towards earlier treatment initiation was observed. As noted earlier in the discussion, very few mothers in this sample were treated with single-dose nevirapine for PMTCT. Both findings are likely due to the fact that the PMTCT guidelines are being talked about and disseminated throughout Kenya. If this trend continues, it is probable that an increase in individuals treated in accordance with WHO Option A will be observed. However, the Kenyan government is now committed to scaling up treatment to Option B/B+ which will be notably more difficult given the low percentage (1.7%) of infants in this study that were treated in accordance with WHO Option B.

In addition, antiretroviral treatment in the developing world is often dependent on external factors such as funding from global health organizations or NGOs that should be taken into consideration. Kenya's HIV/AIDS program has a budget of 629 million dollars with 510 million of that budget coming from the United States PEPFAR program, 34 million from the government of Kenya, and an additional 32.5 million coming from the Global Fund to Fight AIDS, Tuberculosis, and Malaria (NACC, 2011). With Kenya's population growing at a more rapid pace than other sub-Saharan African countries (World Bank, 2010), Kenya will need to at minimum maintain and perhaps increase this funding to fully scale up treatment options in the future (NACC, 2011).

Another factor that will be worth examining in the future is the disparities between the urban and peri-urban or more rural clinical locations. According to World Bank (2010) estimates, 78% of Kenyans reside in rural areas. In this study, women at the Pumwani and Mathare hospitals in urban Nairobi received PMTCT at higher percentages than at the peri-urban locations of Kapsabet and Kericho in western Kenya. Women in the peri-urban locations may be traveling to receive clinical care from far-reaching rural areas. Transportation has been cited in several studies (Bwirire et al, 2008, Delva et al., 2010, Hassan et al., 2012, Otieno et al., 2010) as a barrier to engaging in PMTCT or EID care. Women in rural areas, in particular, report struggling with transportation issues as a result of having to travel to a more central or urbanized setting. Collecting information regarding distance travelled to clinical appointments may be advantageous in the future to determine if there is a considerable difference between the urban and rural mothers in this sample. Additionally it may be worthwhile to examine access to treatment among the particular urban and peri-urban clinics to determine if the peri-urban or rural locations have more difficulty in accessing antiretroviral therapy. Drug shortages have been

identified as a deterrent to treatment in the past and individuals have reported being unable to obtain prescribed regimens (NACC, 2011).

An analysis examining the lost to follow-up infants would be relevant in the future as some of the infants enrolled in EID care were not tested for HIV and did not engage in follow-up. Future research with the HITSystem© plans to address this issue as information regarding lost to follow-up infants has been collected since the onset of this study.

### **5.3) Conclusion**

With the introduction of updated guidelines for PMTCT in 2010, the World Health Organization provided developing countries with streamlined options for establishing a new standard of care for PMTCT. By adapting the guidelines, countries like Kenya have the ability to more effectively hone in on their own resource bases to determine possible treatment outcomes. In assessing WHO and NASCOP guidelines, this study determined that the majority of the 853 mother-infant pairs in this sample are being treated in accordance with the Kenya-specific NASCOP guidelines. However, significant work needs to be done to improve uptake of Options A and B/B+. While it is likely that some clinical, patient and societal barriers exist, results of this study indicate a significant trend towards early initiation of PMTCT treatment among the hospitals in this study.

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Figure 1: WHO clinical staging of HIV disease in adults and adolescents

Clinical stage 1
<ul style="list-style-type: none"> <li>• Asymptomatic</li> <li>• Persistent generalized lymphadenopathy</li> </ul>
Clinical stage 2
<ul style="list-style-type: none"> <li>• Moderate unexplained weight loss (under 10% of presumed or measured body weight)</li> <li>• Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)</li> <li>• Herpes zoster</li> <li>• Angular cheilitis</li> <li>• Recurrent oral ulcerations</li> <li>• Papular pruritic eruptions</li> <li>• Seborrhoeic dermatitis</li> <li>• Fungal nail infections</li> </ul>
Clinical stage 3
<ul style="list-style-type: none"> <li>• Unexplained severe weight loss (over 10% of presumed or measured body weight)</li> <li>• Unexplained chronic diarrhea for longer than 1 month</li> <li>• Unexplained persistent fever (intermittent or constant for longer than 1 month)</li> <li>• Persistent oral candidiasis</li> <li>• Oral hairy leukoplakia</li> <li>• Pulmonary tuberculosis</li> <li>• Severe bacterial infections (e.g. pneumonia, empyema, meningitis, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)</li> <li>• Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis</li> <li>• Unexplained anaemia (below 8 g/dl ), neutropenia (below <math>0.5 \times 10^9/l</math>) and/or chronic thrombocytopenia (below <math>50 \times 10^9/l</math>)</li> </ul>
Clinical stage 4
<ul style="list-style-type: none"> <li>• HIV wasting syndrome</li> <li>• <i>Pneumocystis jiroveci</i> pneumonia</li> <li>• Recurrent severe bacterial pneumonia</li> <li>• Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site)</li> <li>• Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)</li> <li>• Extrapulmonary tuberculosis</li> <li>• Kaposi sarcoma</li> <li>• Cytomegalovirus disease (retinitis or infection of other organs, excluding liver, spleen and lymph nodes)</li> <li>• Central nervous system toxoplasmosis</li> <li>• HIV encephalopathy</li> <li>• Extrapulmonary cryptococcosis including meningitis</li> <li>• Disseminated nontuberculous mycobacteria infection</li> </ul>

- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated mycosis (histoplasmosis, coccidiomycosis)
- Recurrent septicaemia (including nontyphoidal *Salmonella*)
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

*Note.* From “Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants.” World Health Organization, 2010, p. 27-28.

Figure 2: WHO and NASCOP 2010 guidelines for PMTCT

	WHO 2010 Guidelines	NASCOP 2010 Guidelines
	Prophylaxis (Women with CD4 count >350 cells/mm <sup>3</sup> )	Prophylaxis (Women with CD4 count >350 cells/mm <sup>3</sup> )
Option A	<p><b>Antepartum:</b> AZT starting as early as 14 weeks gestation.</p> <p><b>Intrapartum:</b> at onset of labor, sdNVP and first dose of AZT/3TC.</p> <p><b>Postpartum:</b> daily AZT/3TC through 7 days postpartum.</p>	<p><b>Antepartum:</b> AZT starting as early as 28 weeks gestation.</p> <p><b>Intrapartum:</b> at onset of labor, sdNVP and first dose of AZT/3TC.</p> <p><b>Postpartum:</b> daily AZT/3TC through 7 days postpartum.</p>
Option B	Triple ARVs starting as early as 14 weeks gestation and continued intrapartum and through childbirth if not breastfeeding or until 1 week after cessation of all breastfeeding.	
Option B+	Regardless of CD4 count, triple ARVs starting as soon as diagnosed, continued for life.	

*Note.* Adapted from “Programmatic update: Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants.” World Health Organization, 2012, p. 2. and “Guidelines for prevention of mother to child transmission of HIV/AIDS in Kenya.” Kenya Ministry of Health, National AIDS and STI Control Programme, 2010, p. 46-47.

Figure 3: Map of Kenya with study hospitals

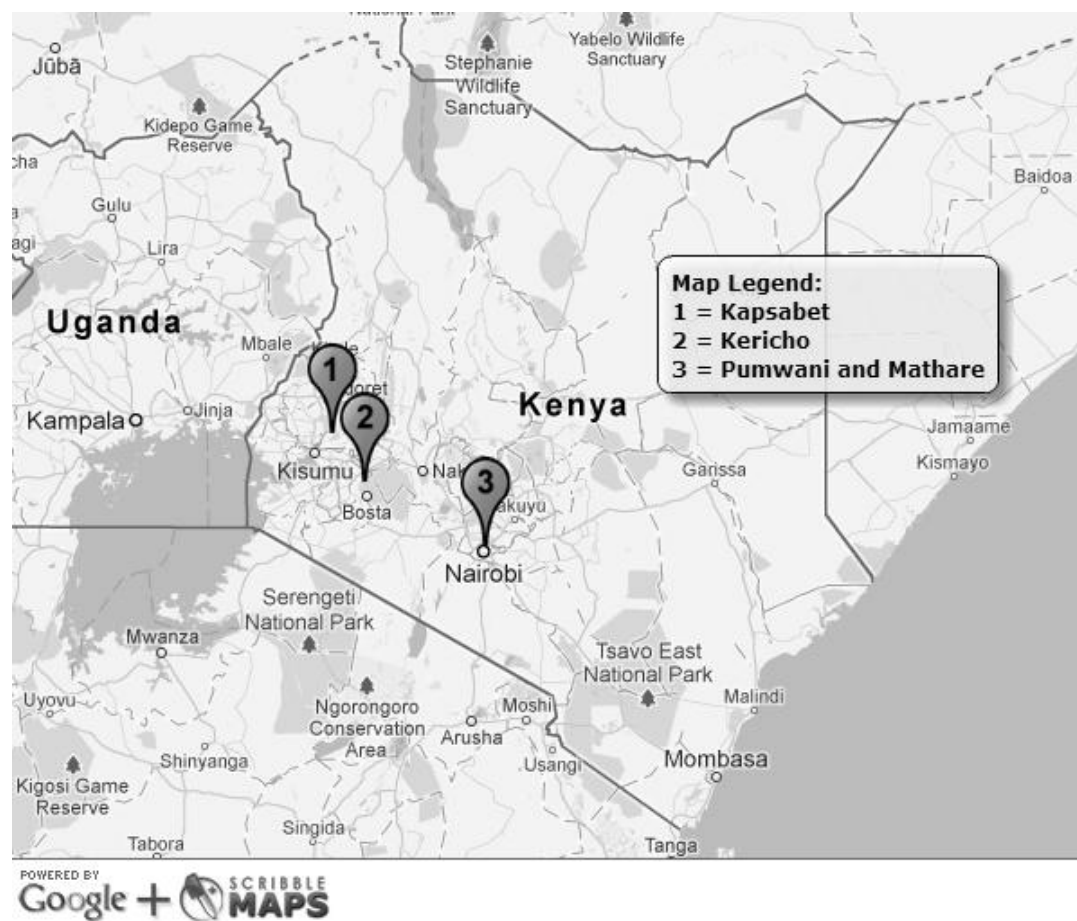


Figure 4: Mean week of PMTCT treatment initiation by year (2010-2012)

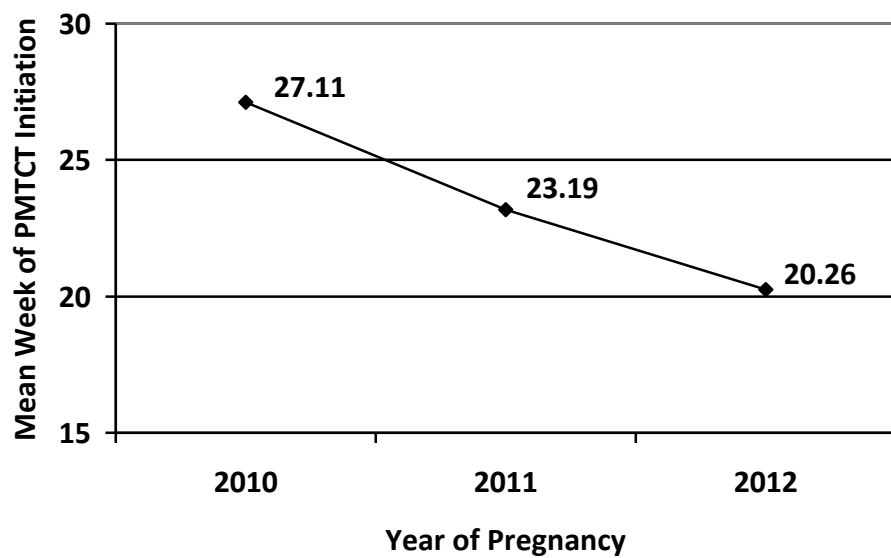


Figure 5: Mean week of PMTCT treatment initiation by hospital

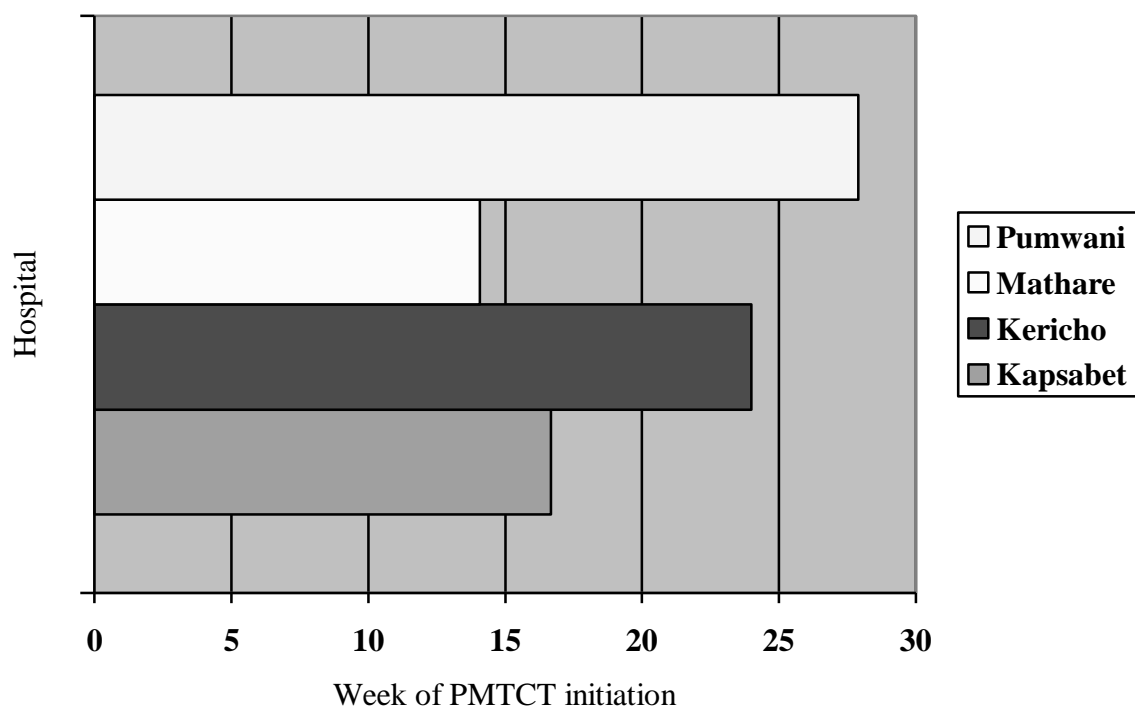


Table 1: Description of sample by hospital

Hospital	Kapsabet	Kericho	Mathare	Pumwani	Total
Total sample of mother-infant pairs	137 (16.06%)	127 (14.89%)	124 (14.54%)	465 (54.51%)	853 (100%)
Mother on PMTCT	88 (64.23%)	72 (56.69%)	112 (90.32%)	454 (97.63%)	726 (85.11%)
Infants tested for HIV	134 (97.81%)	109 (85.83%)	108 (87.10%)	464 (99.78%)	815 (95.55%)
Infants testing HIV+	12 (8.96%)	3 (2.75%)	15 (13.89%)	11 (2.37%)	41 (5.03%)
Infants with an indeterminate HIV test result	1 (0.75%)	1 (0.92%)	1 (0.93%)	0 (0%)	3 (0.37%)



Table 2: Description of hospitals meeting NASCOP, WHO Option A, and WHO Option B PMTCT guidelines

Hospital N = total minus missing	Number (%)* meeting NASCOP 2010 Guidelines	Number (%)* meeting WHO 2010 Guidelines Option A	Number (%)* meeting WHO 2010 Guidelines Option B	Missing or Unknown Regimen (n = 100/853)
Kapsabet n = 110	46 (41.8%)	13 (11.8%)	13 (11.8%)	27 (19.7 %)
Kericho n = 105	32 (30.5%)	14 (13.3%)	0 (0%)	22 (17.3%)
Mathare n = 87	63 (72.4%)	34 (39.1%)	0 (0%)	37 (29.8%)
Pumwani n = 451	436 (96.7%)	2 (0.4%)	0 (0%)	14 (3.0%)
Total N = 753	577 (76.6%)	63 (8.4%)	13 (1.7%)	100 (11.7%)

Table 3: Breakdown of adherence to NASCOP, WHO Option A, and WHO Option B PMTCT guidelines by hospital

Hospital	Guideline	Meets guidelines	Late treatment initiation	Insufficient regimen	No intervention
Kapsabet n = 110	NASCOP	46 (41.8%)	15 (13.6%)	0 (0%)	
	WHO Option A	13 (11.8%)	48 (43.6%)	0 (0%)	49 (44.5%)**
	WHO Option B	13 (11.8%)	0 (0%)	48 (43.6%)	
Kericho n = 105	NASCOP	32 (30.5%)	14 (13.3%)	4 (3.8%)	
	WHO Option A	14 (13.3%)	32 (30.5%)	4 (3.8%)	55 (52.4%)**
	WHO Option B	0 (0%)	0 (0%)	50 (47.6%)	
Mathare n = 87	NASCOP	63 (72.4%)	11 (12.6%)	1 (1.1%)	
	WHO Option A	34 (39.1%)	40 (46.0%)	1 (1.1%)	12 (13.8%)**
	WHO Option B	0 (0%)	0 (0%)	75 (86.2%)	
Pumwani n = 451	NASCOP	436 (96.7%)	4 (0.9%)	0 (0%)	
	WHO Option A	2 (0.4%)	438 (97.1%)	0 (0%)	11 (2.4%)**
	WHO Option B	0 (0%)	10 (2.2%)	95.3%	
Total N =753*	NASCOP	577 (76.6%)	44 (5.8%)	5 (0.7%)	
	WHO Option A	63 (8.4%)	558 (74.1%)	5 (0.7%)	127 (16.9%)**
	WHO Option B	13 (1.5%)	10 (1.3%)	603 (80.1%)	

\*Note. Total indicates percentage minus n=100 cases with unknown or missing regimen information.

\*\*Note. Individuals receiving no intervention are the same across all three guidelines.

Table 4: One-way ANOVA for mean week of treatment initiation by year 2010-2012

Year	N	Mean	Standard Deviation	Standard Error	95% CI	
					Lower Bound	Upper Bound
2010	180	27.11	5.24	.391	26.33	27.88
2011	512	23.19	10.61	.469	22.27	24.11
2012	34	20.26	11.77	2.019	16.16	24.37
Total	726	24.02	9.80	.364	23.31	24.74
		SS	df	F	<i>p</i>	
Between Groups		2546.367	2	13.725	.000	
Within Groups		67066.235	723			
Total		69612.602	725			

Table 5: Post-hoc analyses of ANOVA with Tukey HSD

Year Pregnancy	Year Pregnancy	Mean Difference	<i>p</i>	95% CI	
				Lower Bound	Upper Bound
2010	2011	3.916*	.000	1.96	5.88
	2012	6.841*	.000	2.61	11.07
2011	2010	-3.916*	.000	-5.88	-1.96
	2012	2.925	.200	-1.08	6.93
2012	2010	-6.841*	.000	-11.07	-2.61
	2011	-2.925	.200	-6.93	1.08

\**Note.* The mean difference is significant at the 0.05 level.