Adherence to the prevention of mother-to-child transmission of HIV (PMTCT) program among women living with HIV in Zambia

ザンビア共和国における HIV 陽性女性の
母子感染予防プログラムへのアドヒアランス

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List of Acronyms

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ART service	HIV care and treatment service
ARV	Antiretroviral
AZT	Zidovudine, Azidothymidine
CD4	Cluster of Differentiation antigen 4 lymphocyte
CI	Confidence Interval
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
JICA	Japan International Cooperation Agency
MCH	Mother and Child Health
NVP	Nevirapine
PCR	Polymerase Chain Reaction
PHC	Primary Health Center
PLWH	People Living With HIV

PMTCT	Prevention of Mother-to-Child Transmission of HIV
SD	Standard Deviation
sd-NVP	Single Dose Nevirapine
TBA	Traditional Birth Attendant
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization
YLL	Years of Life Lost
Zambia	The Republic of Zambia

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Abstract

Introduction

Optimal adherence to antiretroviral (ARV) is essential for preventing mother-to-child transmission of HIV. Since the Zambian government has revised the national guidelines in 2010, no studies have assessed ARV adherence. This study aimed to examine a probability of adherence to ARV and identify the risk factors for non-adherence in the PMTCT program.

Methods

A prospective cohort study was conducted in Chongwe district, from June 2011 to October 2012. Four-days self-report ARV adherence was assessed among 321 HIV-positive mothers during pregnancy, 1 week, 6 weeks, and 24 weeks postpartum. Probability of adherence was calculated using Kaplan-Meier survival methods, and Cox proportional hazard regressions were performed to identify risk factors for non-adherence controlling for the effects of loss to follow-up.

Results

A high incidence of non-adherence was observed in HIV-positive mothers. Especially, mothers attending referral health center were more likely to be non-adherent, compared

with mothers attending primary health centers (PHCs) with ART services (hazard ratio (HR): 0.71, 95% CI: 0.57-0.88) and those attending PHCs without ART services (HR: 0.58, 95% CI: 0.46-0.74). Mothers newly diagnosed as HIV-positive showed a higher risk for non-adherent (HR: 1.24, 95% CI:1.03-1.50).

Conclusion

This study found poor ARV adherence in the PMTCT program due to high incidence of loss to follow-up. Expanding ART services at all PHCs should be considered. Early HIV testing and treatment before pregnancy and couple HIV testing and counseling are potential strategies to improve adherence to the PMTCT program.

Key words

Prevention of mother-to-child transmission of HIV (PMTCT), Antiretroviral (ARV), Adherence, HIV care, Pregnancy

1: Introduction

1-1. Global situation of HIV/AIDS

1-1-1) HIV Epidemic

The global HIV/AIDS epidemic is a leading cause of death. The number of people who were newly infected with HIV was 2.7 million, and the number of people who died due to AIDS-related diseases was 1.8 million in 2010 (1). People living with HIV (PLWH) has continued to increase, reaching 34 million in 2010 due to reductions in AIDS-related deaths (1). Sub-Saharan Africa carries the highest burden of HIV: the proportion of PLWH in this region alone accounted for 68% of the global population of PLWH; 70% of new HIV infections; and 67% of AIDS-related deaths in 2010 (1). Such HIV epidemic has been a substantial barrier to socio-economic development in sub-Saharan Africa.

1-1-2) Children and HIV/AIDS

Infants are at risk of acquiring HIV from the mother in the uterus, during the birthing process, and through breastfeeding (2). Among breastfeeding infants, an estimated 20 to 25% of HIV transmission occurs in utero, 40 to 55% during labor and delivery, 20 to 25% at first two months of life, and 5 to 10% after two months of age (3). Breastfeeding causes an additional risk depending on maternal viral load, advanced immune deficiency, prolonged rupture of membranes, and mastitis (3). Over 90% of pediatric HIV attributes to mother-to-child transmission (2). If any antiretroviral (ARV)

intervention is not used, 15 to 30% of non-breastfeeding infants and 30 to 45% of breastfeeding infants will be at risk of HIV infection (2, 3). In 2010, about 3.4 million children under 15 years were estimated to be living with HIV, 390,000 were newly infected, and 250,000 died from AIDS-related causes (1). About 90% of the HIV-positive children were living in sub-Saharan African countries (1). Meanwhile, improved access to HIV care and treatment has reduced 30% of new pediatric HIV infections from 2001 to 2010, and also 30% of AIDS-related deaths from 2005 to 2010 (1).

1-1-3) Global response to HIV/AIDS

Combating HIV/AIDS is one of the prioritized targets outlined in the Millennium Development Goals. In 2001, the United Nations General Assembly Special Session on HIV/AIDS called for a global commitment to an expansion of antiretroviral therapy (ART) and prevention of mother-to-child transmission of HIV (PMTCT) (1, 4). An increasing demand for fundraising in HIV services spawned the Global Fund in 2002, followed by the United States President's Emergency Plan for AIDS Relief in 2003 (1, 4). Meanwhile, the "3 by 5" and universal access initiatives have accelerated scale-up of HIV prevention, treatment, care and support for tuberculosis patients with HIV, injecting drug users, sex workers, men who have sex with men, pregnant women, and children exposed to HIV in low- and middle-income countries (1, 5). In 2010, WHO revised the guidelines for ART to promote early initiation with an efficacious regimen (6-8). Recent research has built evidence that ART can significantly suppresses viral load and reduce the risk of HIV transmission

from mother to child (9-17) and from HIV-positive partner to HIV-negative partner, delay onset of opportunistic infections and AIDS (18), and prevent tuberculosis disease in HIV-positive individuals (19). Based on such evidence, ART can now play an important role in "treatment as prevention": using ART as a HIV prevention method that significantly reduces the risk of HIV transmission (20). The WHO and UNAIDS undertook the Treatment 2.0 initiative in 2011, which aims to achieve and sustain universal access to ART through expanding point-of-care diagnostics, optimal ARV regimens and other HIV care and treatment services at lower cost, and mobilizing community support (4). The major targets of the Treatment 2.0 initiative are to: 1) eliminate new pediatric HIV infections; 2) decrease tuberculosis-related deaths in people living with HIV by half; and 3) provide ART to 15 million people in need (4). Thus, the PMTCT program has emerged as a substantially prioritized target for its great potential to reduce the global burden of HIV/AIDS.

1-1-4) PMTCT program

The PMTCT program was launched globally in 1998 (2). Since 2011, the PMTCT program has been oriented toward eliminating new pediatric HIV infections and improving maternal and child health and survival (21). To these ends, a four-pronged approach has been taken: 1) primary prevention of HIV infections in young women and reproductive-aged women; 2) family planning to prevent unintended pregnancy; 3) ARV interventions for prevention of vertical transmission to infants; and 4) assuring linkages to care, treatment and follow-up (21). Of the four approaches, ARV interventions can make a direct impact on reduction of mother-to-child transmission (9-17).

To minimize mortality and morbidity in HIV-exposed or –infected infants, the PMTCT program generally adopted a six-combination intervention from pregnancy to breastfeeding period: 1) antenatal HIV testing and counseling; 2) ARV provision to pregnant women diagnosed as HIV-positive; 3) ARV provision for infants born to HIV-positive mothers; 4) early diagnosis of HIV infection among infants; 5) co-trimoxazole provision for HIV-exposed children; and 6) provision of HIV care and treatment to HIV-positive children (1). Opt-out HIV counseling and testing is the initial step in these interventions, as it can identify HIV-positive pregnant women who could receive crucial benefits from ARV intervention for improving their own health and protecting their infants from HIV (22, 23). HIV-positive mothers or their infants need to receive ARV as long as the infants are exposed to the risk of HIV transmission (7). HIV testing is recommended for these children by 4-6 weeks of age, which is essential to facilitate immediate initiation of ART and increase survival of HIV infected infants (24-26). Since access to pediatric HIV care and treatment are limited in high HIV burden countries, the use of co-trimoxazole prophylaxis can reduce the risk of diseases progression and death in HIV-positive children until they initiate ART (27-31). For such benefits, all HIV-exposed infants take co-trimoxiazole until breastfeeding is completely terminated and HIV status is confirmed to be negative (31).

1-1-5) Scale-up of ARV interventions in the PMTCT program

The first PMTCT guidelines on ARV intervention were released by WHO in 2000, later updated in 2004 (32), 2006 (33), and 2010 (7) as the efficacy and safety of ARV regimens were confirmed. A meta analysis of clinical trials conducted in African

countries showed significant efficacy of ARV intervention with transmission rate of 10.6% in intervention arms versus 21.0% in placebo arms (11). Increased ARV coverage has also facilitated a great reduction in mother-to-child transmission at population level. In 2010, for example, 48% of mothers received ARV (excluding single-dose nevirapine [sd-NVP]), 34% of pregnant women eligible for ART received treatment, and 42% of infants received ARV for prophylaxis in low- and middle-income countries (1). As a result, the mother-to-child transmission rate was reduced from 35% to 26% in low- and middle-income countries during the past decade (1). In non-clinical trial settings, ARV interventions also demonstrated a great reduction in the rate of mother-to-child transmission in high HIV prevalence countries (34-38).

1-1-6) WHO 2010 ARV guidelines for PMTCT

The 2010 WHO ARV guidelines were developed to utilize more efficacious ARV interventions in resource-limited settings (7). Proper implementation of the guidelines would reduce the risk of HIV transmission to less than 5% among breastfeeding infants and to less than 2% among non-breastfeeding infants, and will improve maternal and child survival (7). The guidelines recommend two new approaches: 1) HIV positive women eligible for treatment early initiate lifelong ART for preventing HIV transmission and improving their own health, and 2) HIV positive women not eligible for lifelong treatment take ARV prophylaxis to reduce the risk of HIV transmission to their infants from pregnancy, delivery to breastfeeding period (7). The major differences from the 2006 guidelines are ARV eligibility criteria for prescribing treatment or prophylaxis regimen, timing of commencement of antenatal

ARV prophylaxis, and ARV prophylaxis regimen for HIV-exposed infants (7) (Appendix 1).

The 2010 guidelines recommend two ARV regimen options: Option "A" and Option "B" (Appendix 2). Both options recommend that pregnant women with CD4+ lymphocyte (CD4) counts less than 350 cells/mm^3 or at clinical stage 3 or 4 commence a lifelong ART regimen, and pregnant women not eligible for treatment commence an ARV prophylaxis regimen (7). For mothers not eligible for treatment, Option A recommends initiation of zidovudine (AZT) from 14 weeks of gestation, sd-NVP at labor, and the addition of lamivudine from delivery to 7 days post-delivery (7). Option B recommends initiation of triple ARVs prophylaxis from 14 weeks of gestation until the one week after completing breast-milk (7). For infants, Option A recommends that breastfed infants ingest NVP from birth to 1 week after the complete weaning of breast-milk, non-breastfed infants ingest sd-NVP plus AZT or NVP for the first 4 - 6 weeks, and infants born to mothers on ART are administered NVP or AZT for the first 4 - 6 weeks, while Option B suggests that infants take NVP or AZT only for the first 4 - 6 weeks since mothers take ART (7). Both options are equally efficacious in pregnant women with CD4 counts over 350 cells/mm^3 (39). However, Option A is advantageous in resource-limited countries, due to lower drug costs and dispensing of the same ARV drugs used in the 2006 guidelines (39).

Guidelines for feeding practices were also updated in 2009. Mothers living with HIV are recommended to undertake exclusive breastfeeding from birth to 6 months, then introduce supplementary food, and continue breastfeeding until 12 months (7, 40). To maximize the efficacy of the guidelines, both mothers and their infants need to be adherent to ARV medication and feeding practice, otherwise failure to adhere to the

guidelines may increase the risk of malnutrition, morbidity and mortality caused by HIV and other infectious diseases (9, 16, 40, 41). The guidelines offer the opportunity to control mother-to-child transmission, if it can be implemented properly. However, multiple operational challenges occur in resource-limited countries with a high burden of HIV, such as the Republic of Zambia (Zambia).

1-2. HIV/AIDS in Zambia

1-2-1) Epidemiology

Zambia is one of the highest HIV prevalence countries. It is located in the southern part of Africa, with a population of 13 million in 2010 (42). The first case of HIV infection was reported in 1984, after which HIV prevalence rapidly grew to a peak of 16% in the mid-1990s (43). HIV/AIDS is the top-ranked cause of years of life lost (YLLs), accounting for 15% of all YLLs in 1990, and increasing to 20% of all YLLs in 2010 (44). In 2007, HIV prevalence among adults aged 15-49 years was about 14% (42). Over 900,000 people were estimated to be living with HIV/AIDS, about 80,000 of whom were newly infected, and the total number of AIDS-related deaths was about 42,000 in 2009 (43). Casual sex **(**defined as "sex with multiple partners as well as with partners who are neither spouses nor cohabiting") is a major cause of HIV infection, accounting for more than 70% of new infections (42, 45). An estimated 23% of adults aged 15-49 years were tested for HIV in 2009 (42). Men were more likely to have multiple and/or concurrent partners than women (14% compared to 1%), and 27% of men and 33% of women reported condom use in sexual intercourse with multiple and/or concurrent partners (42).

1-2-2) Pediatric HIV/AIDS in Zambia

Mother-to-child-transmission is a major cause of pediatric HIV infection in Zambia. HIV infections in children under 14 years accounts for 10% of all HIV infections in Zambia (43), slightly lower than the average of 13% in sub-Saharan African countries (1). However, only 31% of the children received ART in 2010 (46). Every year, about 80,000 infants are born at risk of acquiring HIV from their mothers (47), and HIV caused an estimated 12% of deaths in children under 5 years in 2010 (46). In children aged less than 14 years, the number of new infections has fallen from 21,189 in 1996 to 9,196 in 2009 (43). Estimated AIDS-related child mortality also decreased from 14,681 in 2003 to 7,282 in 2009 (43). Although progress has been made on reducing new pediatric HIV infections and related deaths, further effort is needed to achieve the goal of eliminating new pediatric infections by 2015. A key to this effort is further scale-up of the PMTCT program across the country.

1-2-3) The PMTCT program in Zambia

Zambia introduced the PMTCT program in 1999, and has been rapidly scaling up over the past decade (47). Such efforts reduced the incidence of mother-to-child transmission from 24% in 2009 to 11% in 2011 (46). In 2011, 97% of pregnant women underwent HIV testing, and 85% of HIV-positive pregnant women received ARV (42). Of the available ARV regimens, 11% of women received only sd-NVP, 75% were prescribed a AZT prophylaxis regimen, and 14% had taken ART in 2011 (42). Uptake

of PMTCT services in infants born to HIV-positive mothers remains limited, compared with HIV-positive pregnant women. In 2011, only 36% of the infants received ARV, 37% received co-trimoxazole, and 27% underwent virological HIV testing within two months of age (42).

The new national guidelines (Appendix 3) were developed by the Zambian Ministry of Health in 2010 based on Option A of the WHO 2010 guidelines, and introduced across the country in 2011(47). However, several challenges in adherence to the PMTCT program have emerged. For example, delayed first antenatal attendance may cause mothers to start ARV later than the recommended timing of 14 weeks gestation, because the first antenatal clinic attendance occurs at an average 20 weeks gestation (48). Continuing ARV prophylaxis until the end of breastfeeding can also be difficult for mothers not eligible for treatment as only half of mothers attend postnatal check-up (48). Barriers to providing full PMTCT services include poor geographical accessibility, lack of male involvement, limited access to early infant diagnosis, human resource shortages, stock-out of ARVs, and poor linkages from PMTCT to further examination and treatment at ART clinics (43).

1-3. ARV adherence

1-3-1) Importance of assessing ARV adherence

ARV interventions for PMTCT should not be evaluated only by ARV coverage at the population level. It should be also evaluated by ARV adherence at individual level for the period that infant is exposed to a risk of HIV transmission. This is because adherence should be strictly observed in order to maximize treatment benefits for

reducing viral load, and preventing drug resistance (49-51). For PMTCT, suppressed maternal viral load can significantly contribute to improve maternal health and reduce the risk of vertical transmission to infants (52). Although few studies have reported optimal levels of ARV adherence for PMTCT, a minimum 95% level of adherence is generally required to maintain virologic suppression (53, 54).

1-3-2) ARV adherence in various populations

ARV adherence has been examined in various target populations and study settings, using different measurements. Two meta-analyses on ARV adherence reported that an estimated 74% of pregnant women in low- and middle- income countries reached adequate levels of adherence (41), compared with 77% of the general population on ART in sub-Saharan African countries (55). Only a few studies have compared ARV adherence between pregnant women and non-pregnant women. In Brazil, for example, pregnant women showed greater adherence than non-pregnant women (56). In South Africa, women who had previously received PMTCT services were more likely to be adherent (51). In the meta-analysis of maternal ARV adherence in the PMTCT program, pregnancy was the only factor positively associated with adherence, possibly due to maternal concerns about fetal health and vertical transmission (41). Of the 51 selected studies, however, the majority of studies assessed adherence in the antenatal period alone, and only eight studies examined adherence in the both antenatal and postnatal periods (41). Of the eight studies, only two studies were conducted in sub-Saharan Africa (41, 57, 58). Thus, further investigation is needed to

demonstrate ARV adherence during both the antenatal and postnatal period in sub-Saharan Africa.

1-3-3) Adherence before and after delivery in high-income countries

Poor ARV adherence rates have been reported in assessments of the pregnancy and postnatal periods in the United States (Appendix 4). For example, adherence rates in antenatal women were 61 to 80%, and 44 to 66% in postnatal women (59-65). Non-adherence was associated with minority group membership, residence area, being teenaged (59), asymptomatic HIV condition, and having two or more additional children (61), daily medication taken more than twice (62), advanced disease stage, higher viral load, multiple HIV-related symptoms, alcohol consumption, and times of clinical evaluation (65). On the other hand, better adherence was associated with less advanced disease stage, feeling happy (64), never having missed a prenatal vitamin dose, non-use of illicit drug (60, 64), having a social support network and disclosure of HIV status (61, 63). ART initiation before or after pregnancy was inconsistently associated with adherence (59, 64). Although these studies provided important evidence about ARV adherence for PMTCT in the United States, maternal backgrounds, development stage and epidemic context differ between the United States and sub-Saharan African countries. Thus, it is important to examine ARV adherence for PMTCT separately in sub-Saharan Africa countries.

1-3-4) Perinatal adherence in sub-Saharan Africa

Until the AZT prophylaxis regimen was established, taking sd-NVP by mothers and prescribing NVP to their infants had been the proxy indicators for ARV adherence in the PMTCT program. A number of studiers have reported a wide range of adherence rates: 42 to 94% in mothers, and 24 to 91% in their infants (Appendix 4) (66-75). In these studies, home delivery was an especially common risk factor for non-adherence (67-69, 72, 75, 76). In Tanzania and Uganda, NVP administration to infants was associated with older maternal age, secondary school education, Catholic religion, and receiving a counseling about PMTCT in a hospital (68). In another study from Uganda, women who were aged over 25 to 34 years, who came from the study sites, who visited an antenatal clinic at advanced gestation, and who were on ART were more likely to be adherent (71). In Kenya, non-adherence was associated with fewer antenatal clinic attendance, younger maternal age, and single mothers (69). In the study, adherent mothers were more likely to receive ARV for infants (69). In Rwanda, women who were not married, who had less educational experience, who had HIV test after first antenatal clinic attendance, who attended antenatal clinics fewer times, and who have not disclosed their HIV-positive status to someone aside from a partner were less likely to be adherent (70). In Zimbabwe, non-adherence was associated with no experience of secondary education, multi-parity, and non-disclosure of HIV status, while adherence was associated with previous experience of the PMTCT program, and NVP given beforehand at an antenatal clinic (72). In South Africa, adherence was associated with better knowledge on PMTCT program, full-term delivery, disclosure of HIV status to other, talking with partner about NVP, and having asked partner to undergo HIV testing (73). In four sub-Saharan countries including Zambia, non-adherence to NVP was

associated with maternal age between 26 to 30 years, multi-gravidity, fewer antenatal clinic visits, vaginal delivery, and sd-NVP regimen compared with ART (74). Additionally, a qualitative study from South Africa showed that elements of health workers' health care performance, such as giving incorrect instructions about medication and not supplying NVP tablet, affected non-adherence (77).

In Zambia, several studies have assessed NVP adherence, and showed a wide range of adherence with rates between 43-94% (66, 67, 74, 78-81). Maternal non-adherence was associated with a longer interval between HIV testing and delivery (66), less than high school-level education, lower newborn birth weight (67), illiteracy (78). Experience of prior fetal or infant death was associated with higher uptake of NVP (78). An intervention to prescribe NVP after testing HIV and assessing sd-NVP adherence in labor wards was associated with increased NVP uptake (81). Meanwhile, non-adherence in infants was associated with infants who were born at a tertiary hospital, those who with lower five-minute Apgar scores, and those who subsequently died within 28 days of age (67).

1-3-5) Adherence before and after delivery in sub-Saharan Africa

Since the ARV prophylaxis regimen was introduced in sub-Saharan Africa in recent years, only a few studies have assessed ARV adherence during pregnancy and post-delivery (Appendix 4). These studies have shown the various rates of adherence to the regimen. In Kenya, a mean adherence level by pill count was 96% under clinical trial setting (57). In Tanzania, adherence at a greater than 95% level was reported among 50% of pregnant women, 42% of mothers during intrapartum period in hospital,

and 19% of their infants at postpartum at hospital, and only one mother-infant pair over the observed period (58). In South Africa, for example, the four-day complete adherence rate was 61% in the antenatal and 86% in the postnatal period (82). In another study from South Africa, 61% of pregnant women achieved over 95% adherence for the entire prophylaxis period (83). In Nigeria, 81% of pregnant women achieved adherence at a greater than 95% level (84).

Disclosure of HIV status was a major concern affecting adherence among pregnant women (58, 82-84). In Tanzania, younger maternal age and having no income-generating activity were risk factors for missing ARV prophylaxis during pregnancy (58). Early enrolment in PMTCT services was also a risk factor for missing antenatal ARV prophylaxis due to a time gap between the first antenatal clinic attendance and ARV initiation after 28 weeks gestation (58). In South Africa, fewer experiences of discrimination and presence of partner involvement in the PMTCT were associated with ARV adherence (82). On the other hand, misunderstanding of the ARV regimen, ARV use by relatives, domestic violence, and poverty influenced non-adherence (83). In the intra- and postpartum periods, non-adherence was affected by unsupportive staff performance (58). In Nigeria, non-adherent women showed frequently lacked a treatment supporter, while adherent women reported high motivation for protecting their infants from HIV transmission (84). In Zambia, there is no available study assessing adherence before and after delivery.

1-3-6) Loss to follow-up in the PMTCT program

Loss to follow-up has been a crucial concern that undermines adherence to ARV, and limits the optimal outcome of PMTCT program (23, 75). In Zambia, poor postnatal attendance and low coverage of postnatal PMTCT program (e.g. prescribing ARV prophylaxis and virological HIV testing for infants) imply that loss to follow-up is a primary challenge in the PMTCT program (42, 48). In rural Malawi, 80% of pregnant women dropped out of the PMTCT program at six months postpartum (85). In Tanzania, 40% of pregnant women did not return to a hospital after delivery (58). In Ethiopia, 30% of infants were lost to follow-up by six months post-delivery (86). In Uganda, 62% of postnatal mothers did not return to the scheduled PMTCT program at six to eight weeks postpartum (87). In South Africa, 40% of HIV-exposed infants were lost to follow up within 28 weeks postpartum (88). Prior attendance to postnatal check-up, having phone contact, Christianity (87), and earlier antenatal clinic attendance (88) were associated with retention in the postnatal PMTCT program. Despite such high incidence of loss to follow-up, few studies have assessed ARV adherence controlling for its negative effect on adherence. Thus, the effect of loss to follow-up should be taken into account in evaluating PMTCT programs for a more realistic estimation of the outcomes (89).

1-4. Justification of the study

Drug treatment interventions such as ARV prophylaxis and ART are a principal strategy for the prevention of mother-to-child transmission of HIV. To maximize the efficacy of the ARV intervention, it is crucial for mothers to attend the PMTCT

program regularly and take ARV with a sufficient level of adherence. Since the WHO 2010 guidelines were released, the ARV regimen has been extended for the first time. However, Zambia and its neighboring countries have not conducted any longitudinal studies on ARV adherence, and no study has ever controlled for the effect of loss to follow-up on ARV adherence.

1-5. Objectives of the study

This study aimed to assess incidence of non-adherence to ARV and to identify risk factors for non-adherence in HIV-positive pregnant women and postnatal mothers until 24 weeks postpartum under the 2010 national guidelines. To assess adherence from the antenatal to postnatal period, the following methods were used:

1. Probability of adherence to ARV was calculated using Kaplan-Meier survival methods;
2. Cox proportional hazard regression was conducted to identify risk factors for non-adherence;
3. Sensitivity analysis was used to test the effect of time definition on hazard ratios.

2: Methods

2-1. Study design

This prospective cohort study was conducted to assess maternal ARV adherence for PMTCT from pregnancy to 24 weeks postpartum. HIV-positive mothers were recruited at anytime from pregnancy to 23 weeks postpartum. They had interviews a maximum of four times including during pregnancy (wave 1), 1 week postpartum (wave 2), 6 weeks postpartum (wave 3), and 24 weeks postpartum (wave 4). These observation points were essential points in the PMTCT program when mothers are expected to attend a health facility.

2-2. Study sites

This study was conducted in Chongwe district, Lusaka province, Zambia (Appendix 5) from June 2011 to October 2012, in collaboration with Japan International Cooperation Agency and National Center for Global Health and Medicine. Chongwe is one of 72 districts, which is a semi-rural area located 45 km away from the capital Lusaka, with an estimated population of 194,000 in 2011. HIV prevalence among pregnant women was 11% in 2008, which significantly declined from 25% in 1994 (90). In the 2007 census, the median length of female school education was 7.3 years, 74% of women had partial or adequate literacy, and 43% of women were employed (48). Over 90% of pregnant women attended antenatal clinics with median gestation on the first attendance of 5.1 months, 78% delivered at health facility, 67% had postnatal check-ups, and 96% have breastfed their newborns (48).

At the beginning of the study, Chongwe district had 39 medical and health facilities, including Chongwe referral health center, Mpanshya mission hospital, and 37 primary health centers (PHCs). Chongwe referral health center supervised 19 PHCs located in the western part of the district, Mpanshya mission hospital was responsible for supervising seven PHCs situated in the eastern part of the district. The remaining five health facilities belonged to a military hospital, and six PHCs were located near Lusaka, thus they referred patients to Lusaka for advanced medical services.

The catchment area of Chongwe referral health center was selected for the study site. In this site, Chongwe referral health center and five PHCs offered HIV care and treatment services (ART services) for general HIV-positive patients, all of which were included in the study. The rest of the 14 PHCs offered PMTCT services but not ART services where thus HIV-positive pregnant women were referred to other health facilities to receive further care and treatment. Of these, five PHCs were included in the study based on the following criteria: being located within 20 km of a neighboring health facility with ART services and Chongwe referral health center, and providing a full set of PMTCT services and delivery care. The remaining nine health facilities were excluded from the study due to small numbers of PMTCT clients, limited PMTCT services, and poor accessibility to advanced medical services. The 11 selected health facilities were categorized into three groups based on health facility level and availability of ARV services: referral health center, five PHCs providing ART services, and five PHCs not providing ART services.

2-3. PMTCT programs in the study site

1) Antenatal period

During the study period, antenatal clinics offered routine PMTCT services at maternal and child health (MCH) wards. These services consisted of group pre-test counseling, opt-out HIV testing, and individual post-test counseling. Within a few hours of rapid HIV testing, results were distributed to each pregnant woman in post-test counseling. Pregnant women who were diagnosed as HIV-positive received sd-NVP tablet for administration during labor and daily AZT drugs for 30 days. During pregnancy, they were recommended to re-attend health facilities for adherence counseling and refilling of prescriptions on a monthly basis. These services were provided by health care workers and trained volunteer workers such as traditional birth attendants (TBA).

2) Labor and delivery period

HIV-positive pregnant women were informed to deliver at health facilities. Women on ARV prophylaxis regimen took sd-NVP, AZT and Lamivudine at labor and delivery. Newborn infants received NVP prophylaxis immediately after birth. At discharge, mothers received AZT and Lamivudine tablets for seven days for themselves and NVP syrup for their infants. Mothers who delivered at home were recommended to come back to the health facility with newborns for prescription of ARV drugs within 48 hours of delivery.

3) Postnatal period

Postnatal ARV protocols were determined by the maternal ARV regimen and feeding options. Based on this, health care workers or trained volunteers instructed the mothers in postnatal medication and appropriate feeding practice. If mothers were not on ART, their infants were given NVP syrup throughout the breastfeeding period. If mothers took ART or did not breastfeed, their infants ceased NVP at six weeks of age. In addition to NVP prophylaxis, these infants initiated co-trimoxazole from six weeks of age. These infants were recommended to take a HIV polymerase chain reaction (PCR) testing at six weeks and six months of age. The PCR samples were sent to Kalingalinga laboratory in Lusaka. After a few weeks, the referral health center received all test results, and health workers from each PHC came to pick up their clients' results. Then, they informed the HIV status of infants to their mothers at the postnatal PMTCT clinic.

4) Referral from PMTCT to ART services

HIV-positive pregnant women need to be referred to ART clinic for receiving further HIV care and treatment. At Chongwe referral health centers, HIV-positive women were tested for CD4 count immediately after diagnosis of HIV at MCH wards, and referred to an ART clinic. At PHCs with ART services, HIV-positive pregnant women were instructed to re-attend health facilities on the day when the ART clinic was opened. Then, they were tested for CD4 count on the first ART clinic visit, and received care and treatment accordingly. At PHCs without ART services, health care workers gave a referral letter to HIV-positive pregnant women, and instructed them to visit the nearest ART clinic.

The referral health center was the only facility affiliated with a laboratory, where CD4 counts were analyzed, and the results were reported to MCH wards through the ART clinic. Meanwhile, PHCs with ART services sent CD4 blood samples to the Kalingalinga laboratory, and received the result after two or more weeks. Clinical information of all ART patients in the district was managed using an electronic database system (Smartcare) at Chongwe referral health center, and patient files were stored at ART clinics in health facilities.

All the PMTCT and ART services were provided for free of charge by the Zambian government. During study period, the 11 health centers had never run out of ARV drugs for mothers and infants.

2-4. Study population

In the 11 target health facilities, 3744 women were tested for HIV under the PMTCT program, and 415 were diagnosed as HIV-positive from January to December 2011. Selection criteria for the study participants were: (1) those who were living with HIV; (2) those who were expected to deliver from January 2011 to September 2012; (3) those who received PMTCT services under the new guidelines at enrolment in the study; and (4) those who gave written consent to study participation at recruitment. Exclusion criteria were: (1) those who had already decided to transfer to different health facilities at recruitment; (2) those who were seriously sick; and (3) those with mental illness. Based on these criteria, 389 women were recruited from July 2011 to March 2012, but 68 mothers were excluded from analysis due to the following reasons: 29 mothers did not complete any questionnaires; 29 mothers enrolled in the study later than

6 months postpartum; 8 mothers had abortion or still births; and 2 mothers had stopped breastfeeding at recruitment. Overall 321 mothers were included in the analysis.

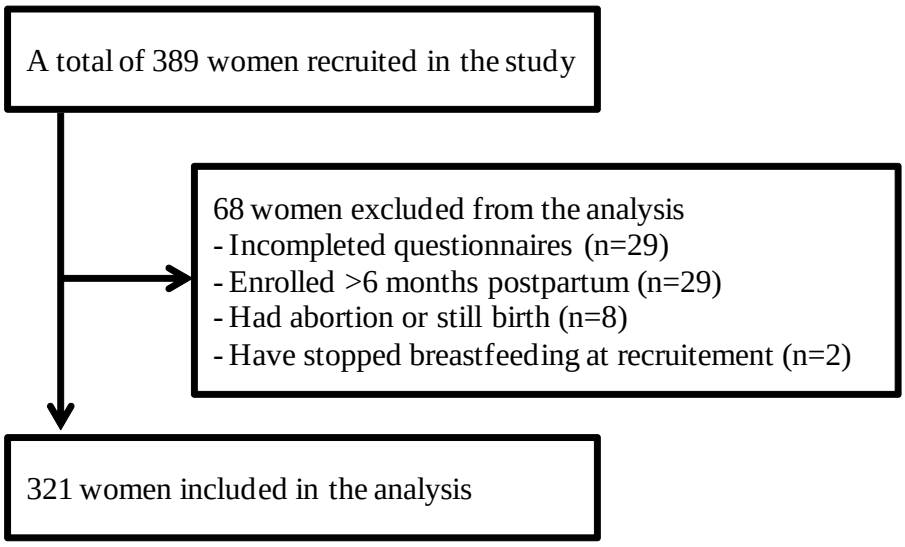


Figure 1. Study participants.

2-5. Study tools

This study used interview-based and clinical record-based tools for data collection. Structured questionnaires were administered at face-to-face interview, and data was also collected from PMTCT-related registers, personal medical files of ART clinic patients, and the electronic database of ART clinic patients (Appendix 6). The questionnaire was developed using generic tools for HIV-related operational research by the WHO (91), the questionnaire utilized in the 2007 Zambia Demographic and Health Survey (48), antenatal cards and children's clinic cards issued by the Zambia Ministry of Health, and a self-report instrument for ARV adherence developed by the Adult AIDS Clinical Trials Group (92-94).

The survey questionnaires collected the following information on maternal characteristics: age, educational level, marital status, timing of HIV diagnosis (already diagnosed / newly diagnosed), ARV regimen, timing of study enrolment (during pregnancy / after delivery), internalized stigma, attitudes regarding taking ARV, experience of couple HIV testing and counseling, disclosure of HIV status to partner, HIV status of partner, experience of domestic violence (verbal abuse, physical abuse, and /or being forced to leave home) (95), travel time to access the health facility, breastfeeding status, and ARV adherence of mother and infant. In the analysis, all independent variables were treated as binary variables. Continuous variables, such as age and travel time to access health facility, were divided at the median. Attitudes regarding taking ARV composed of three items: "Taking medication for HIV (ARV) can help keep HIV from being passed to the baby"; "The HIV medication that you are taking makes you healthier"; and "If you do not take medications for HIV (ARV) properly, the medications won't work as well" (96). ARV-related attitudes were divided into two groups by whether a mother agreed with all three items or not.

The survey questionnaires were developed in English first, translated into Nyanja, the major local language in the study site, and back translated into English for confirming the accuracy of the original translation. The questionnaires were reviewed by Zambian experts on the PMTCT program working for Chongwe District Health Office, and the Zambian Ministry of Health. Before initiating the main survey, pilots test were conducted at two health facilities in the study area to assess face validity of the questionnaire.

The PMTCT-related registers were also used including the safe motherhood register, the integrated counseling register, the delivery register, the MTCT labor ward

register, the under five register, and the baby/mother follow-up register. PMTCT-related information included gestational age at the first antenatal visit, date and place of delivery, birth weight, date of HIV diagnosis, dispense of ARV prophylaxis, HIV status of infants, and survival status of mother and infants. The electronic database and medical files of ART clinic patients were reviewed to collect information on ART services including date of enrolment in ART clinic, assessment of CD4 count, date of ART initiation, and ART regimen.

2-6. Operational definition

1) Adherence to ARV

This study used a self-report ARV adherence instrument to assess the study outcome. ARV adherence can be measured by self-report, electronic drug monitoring, pill counts, prescription refilling records, and therapeutic drug monitoring (97). Although each measurement has advantages and disadvantages for assessing ARV adherence, self-report adherence is a validated instrument and shows good correlation with other measurements and HIV viral load (93, 98, 99). In a meta analysis of ARV adherence in PMTCT programs (51 eligible studies), about half of the studies used self-report adherence measurements (41).

Two ARV adherence questions were cited from the ARV adherence questionnaire of the Adult AIDS Clinical Trials Group: 1) the number of days that a mother missed doses for four days prior to the interview; 2) the number of days that the mother followed a medication schedule during the four days before the interview (92-

94). Since optimal clinical response requires ARV adherence at the 95% level (53, 54, 91), ARV adherence status was defined as "non-adherence" if a mother has missed any prescribed drug, or has not followed their prescribing schedule at least once in the past four days to the interview (64, 82). In addition, if a mother was detected as having medication interruption at interview, they were defined as non-adherence. As the guidelines recommended, mothers on ARV prophylaxis regimen were assessed on the basis of their own adherence during pregnancy and adherence in administering NVP to their infants during postnatal period. Mothers on the ART regimen were assessed on the basis of their own adherence over the assessment period.

2) Loss to follow-up

This study set three interviews points after delivery including one week postpartum (wave 2), six weeks postpartum (wave 3), and 24 weeks postpartum (wave 4). However, many participants had delayed attendance. Thus, time ranges for scheduled observations were provided as follows: 1-5 weeks postpartum for wave 2, 6-23 weeks postpartum for wave 3, and 24-52 weeks postpartum for wave 4. If a participant did not come to the interview within the period, she was treated as lost to follow-up for the wave. Loss to follow-up was significantly associated with non-adherence and treatment failure in a previous study in Zambia (100), thus they were also treated as non-adherent in this study. For these subjects, no follow-up intervention was provided and thus reasons for missed interviews were not collected.

2-7. Data collection

The core research team consisted of Chongwe district health officers, experts of Japan International Cooperation Agency, and the author. The team selected one health worker and one trained volunteer in charge of PMTCT program from each health facility. The qualifications for the research assistant were completion of secondary education, and ability to speak several local languages and English fluently. In June 2011, the core research team held a two-day workshop to train research assistants about study protocol, voluntary participation, confidentiality policy, and data collection. The team also conducted on-site training to supervise data collection.

In the main survey, HIV-positive pregnant women and post-delivery mothers were recruited in the study when they attended the PMTCT program. After providing written consent for study participation (Appendix 7), they were officially enrolled in the study. Face-to-face interviews were conducted with all mothers. At the end of each interview, the mothers received the next appointment and a piece of laundry soap for appreciation.

2-8. Statistical analysis

This study followed up participants over a maximum of four interviews: during pregnancy (wave1); 1-5 weeks postpartum (wave 2); 6-23 weeks postpartum (wave 3); and 24-52 week postpartum (wave 4). The incidence of non-adherence to ARV was calculated using the time from the start of an observation to detection of non-adherence (the event). Non-adherence events also included losses to follow-up, reported and

unreported deaths, and right-censorship at the end of the research period (1 October, 2012). The final observation point was the wave 4 interview, at 24 weeks postpartum, or the research end.

In this study, subjects could potentially experience the non-adherence event more than once during the assessment period, so the data record could contain interval-censored records. To deal with multiple events, this study adopted the recurrent event model (101). In addition, because the exact time of non-adherence was unknown, the censorship point was estimated using the midpoint of the previous- and the current observations (102).

In the recurrent event model using midpoint for censorship, an observation was terminated at the midpoint of the previous observation and the observation at which non-adherence was detected. If changes in ARV regimen were detected, the observation was terminated at the observation point and a new observation period was started from the latest observation point. If a participant did not attend a follow-up observation by the end of a wave, the observation was ended at the midpoint of the prior observation and the cutoff point of the wave. Cutoff points were defined as follows: one week postpartum for wave 2; six weeks postpartum for wave 3; and 24 weeks postpartum for wave 4. For example, if a participant had a baseline interview during pregnancy (wave 1) but did not come to the follow-up interview between one week and five weeks postpartum (within wave 2), her first observation was terminated at the midpoint of the date of the wave 1 interview and one week postpartum.

To test the effect of definition of the time point on the outcome, a second analysis was conducted in which regular cutoff points were applied to censored records

to estimate the time-to-event (alternative model). For example, if a participant who had a baseline interview during pregnancy (wave 1) but did not come to the follow-up interview between one week and five weeks postpartum, her first observation was terminated at one week postpartum. Her second observation was then started at one week postpartum. Sensitivity analysis was performed to test the effect of time definition on study outcomes by comparing results for censoring at the midpoint (main model) with the regular cutoff point (alternative model).

Incidence of non-adherence was compared among 11 health facilities using a Log-rank test. The probability of remaining adherent among three facility types was calculated using survival function and was plotted with a Kaplan-Meier survival curve. The proportional hazards assumption was tested using log-log survival plot and Schoenfeld residuals.

The Cox multivariate regression model was tested to identify risk factors for non-adherence in a backward stepwise model-building procedure. The full model included all independent variables. The final model-building process treated independent variables in two groups: those regarded as essential in the study (age, education, marital status, health facility type, timing of HIV diagnosis), based on the reviewed literature and the context of study site (58, 59, 64, 67-72, 74), were retained regardless of significance; and other possible confounders were retained if their p-value was less than 0.05. It was not possible to run Cox proportional hazard regression using shared frailty and robust variance estimates simultaneously, so in these models the potential correlations within individuals were adjusted for using robust variance estimates, as they were considered likely to affect variance estimates more severely than the effect of facilities. Of all assessed models, the main model with essential and

significant covariates was adopted for discussing study findings. Stata SE version 9.2 (Stata Corp., TX) was used in all statistical analysis.

2-9. Ethical considerations

This study was approved by the Research Ethics Committee of the University of Tokyo (Appendix 8), and the Biomedical Research Ethics Committee of the University of Zambia (Appendix 9). At recruitment in the study, the study objective and protocol were explained to all mothers, and written informed consent was obtained from all of them. Face-to-face interviews were conducted in private rooms in health facilities. When interviewers found any problems in maternal and child health, medication and feeding practice, they provided counseling or referred the participant to health care workers for further support. Confidentiality of all collected data was strictly protected.

3: Results

3-1. Basic characteristics of mothers in the PMTCT program

Table 1 shows the basic characteristics of 321 mothers. The referral health center enrolled 130 mothers (40.5%), the five PHCs with ART services enrolled 106 (33.0%) mothers, and the five PHCs without ART services enrolled 85 mothers (26.5%). Half of the mothers (49.8%) were recruited in the study during pregnancy. The mean age of the mothers was 29.2 (SD 6.1) years old, 105 (32.7%) had education above primary level (8 years), and 272 (84.7%) were married or living with a partner. About half of mothers (49.5%) were newly diagnosed as HIV-positive during the pregnancy. At baseline observation, 154 mothers (48.0%) were on ART, and 67 (20.9%) were non-adherent to ARV. One third (33.3%) had internalized-stigma, and 278 (86.6%) showed positive attitudes toward taking ARV. As for partner characteristics, 129 mothers (40.2%) had couple HIV testing and counseling with their partners, 258 (80.4%) had disclosed HIV status to their partners, and 134 mothers (41.7%) had HIV-positive partners, 52 partners (16.2%) were HIV negative, and 135 (42.1%) were of unknown status. Sixty-two mothers (19.3%) reported that they had recently experienced domestic violence. More than half of the mothers (58.3%) traveled more than 60 minutes to access the nearest health centers. Of these basic characteristics, educational level ($p=0.01$), marital status ($p=0.04$), timing of HIV diagnosis ($p<0.01$), timing of study enrolment ($p=0.05$), experience of couple HIV testing and counseling ($p<0.01$), HIV status of partner ($p=0.03$), and travel time to health facility ($P<0.01$) were significantly

different between referral health center, PHCs with ART services, and PHCs without ART services.

Table 1. Subject Characteristics (N=321).

Characteristics	Overall	Facility Type			*p* -value
		Referral Health	PHCs with ART Service	PHCs without ART Service	
N (%)	321	130 (40.5)	106 (33.0)	85 (26.5)	
Age					
≤29	163 (50.8)	64 (49.2)	48 (45.3)	51 (60.0)	0.1
≥30	158 (49.2)	66 (50.8)	58 (54.7)	34 (40.0)	
Education level					
≤Primary	216 (67.3)	76 (58.5)	81 (76.4)	59 (69.4)	**0.01**
≥Secondary	105 (32.7)	54 (41.5)	25 (23.6)	26 (30.6)	
Marital status					
Not married	49 (15.3)	18 (13.9)	11 (10.4)	20 (23.5)	**0.04**
Married	272 (84.7)	112 (86.2)	95 (89.6)	65 (76.5)	
HIV diagnosis					
Already diagnosed	162 (50.5)	68 (52.3)	68 (64.2)	26 (30.6)	**<0.01**
Newly diagnosed	159 (49.5)	62 (47.7)	38 (35.9)	59 (69.4)	
ARV regimen					
Prophylaxis	167 (52.0)	66 (50.8)	49 (46.2)	52 (61.2)	0.1
Treatment	154 (48.0)	64 (49.2)	57 (53.8)	33 (38.8)	
Study enrolment					
During pregnancy	160 (49.8)	55 (42.3)	62 (58.5)	43 (50.6)	**0.05**
After delivery	161 (50.2)	75 (57.7)	44 (41.5)	42 (49.4)	
Baseline ARV adherence					
Adherence	254 (79.1)	102 (78.5)	89 (84.0)	63 (74.1)	0.2
Non-adherence	67 (20.9)	28 (21.5)	17 (16.0)	22 (25.9)	
Internalized stigma					
No	214 (66.7)	84 (64.6)	75 (70.8)	55 (64.7)	0.6
Yes	107 (33.3)	46 (35.4)	31 (29.3)	30 (35.3)	
Attitude on taking ARV					
≤2 items agreed	43 (13.4)	16 (12.3)	16 (15.1)	11 (12.9)	0.8
3 items agreed	278 (86.6)	114 (87.7)	90 (84.9)	74 (87.1)	
Had couple HIV testing and counseling					
No	192 (59.8)	97 (74.6)	46 (43.4)	49 (57.7)	**<0.01**
Yes	129 (40.2)	33 (25.4)	60 (56.6)	36 (42.4)	
Disclosed HIV status to partner					
No	63 (19.6)	21 (16.2)	18 (17.0)	24 (28.2)	0.07
Yes	258 (80.4)	109 (83.9)	88 (83.0)	61 (71.8)	
HIV status of partner					
Negative	52 (16.2)	13 (10.0)	23 (21.7)	16 (18.8)	**0.03**
Positive	134 (41.7)	58 (44.6)	48 (45.3)	28 (32.9)	
Unknown	135 (42.1)	59 (45.4)	35 (33.0)	41 (48.2)	
Domestic violence					
No	259 (80.7)	102 (78.5)	85 (80.2)	72 (84.7)	0.5
Yes	62 (19.3)	28 (21.5)	21 (19.8)	13 (15.3)	
Travel time to health facility (minutes)					
≤59	134 (41.7)	84 (64.6)	21 (19.8)	29 (34.1)	**<0.01**
≥60	187 (58.3)	46 (35.4)	85 (80.2)	56 (65.9)	

Note: Chi-square test.

3-2. Health facility profile

Table 2 shows health facility profiles in 2011. The referral health facility provided antenatal and PMTCT services to the largest number of pregnant women and HIV-positive pregnant women: an average of 19 pregnant women attended antenatal clinic, and four women were confirmed as HIV positive (including those who had already known their HIV-positive status before testing) and enrolled in the PMTCT program at weekly antenatal clinic. In PHCs, three to eight pregnant women attended the weekly antenatal clinic, and at most one of the women was found to be HIV-positive and enrolled in the PMTCT program.

Table 2. Health Facility Profile in 2011.

	Facility Number[a]										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Number of nurses in charge of Maternal and Child Health ward	7	2	1	1	2	3	1	1	1	2	1
Total number of new pregnant women attending the first antenatal clinic (ANC)	999	416	248	333	310	334	248	154	281	198	223
Total number of pregnant women confirmed as HIV positive	199	31	17	30	24	33	22	10	19	10	20
Average number of pregnant women attending the first ANC per week[b]	19.2	8.0	4.8	6.4	6.0	6.4	4.8	3.0	5.4	3.8	4.3
Average number of pregnant women confirmed as HIV positive per week[c]	3.8	0.6	0.3	0.6	0.5	0.6	0.4	0.2	0.4	0.2	0.4

[a]1=referral health center; 2-6=primary health centers with ART service; 7-11=primary health centers without ART service.

[b]Total number of pregnant women attending the first ANC was divided by total times of ANC opened within the year (52 times).

[c]Total number of pregnant women confirmed as HIV positive was divided by total times of ANC opened within the year (52 times).

3-3. Referral of new HIV-positive mothers to ART services

Table 3 shows referral process of 159 mothers newly diagnosed as HIV-positive from the PMTCT program to ART clinics. Mothers attending the referral health center were more likely to have assessed CD4 count than mothers attending the PHCs ($p<0.01$). However, there were no significant differences in enrolment to ART clinic ($p=0.4$) and subsequent ART initiation ($p=0.7$) among the three types of health facility.

Table 3. Referral to ART Service among Mothers Newly Diagnosed as HIV positive (N=159).

	Facility Type			***p* -value**
	Referral Health Center	**PHCs with ART service**	**PHCs without ART service**	
	N (%)	N (%)	N (%)	
Newly diagnosed as HIV positive	62	38	59	
Assessed CD4 count	55 (88.7)	20 (52.6)	26 (44.1)	**<0.01**
Enrolled in ART clinic	26 (41.9)	21 (55.3)	30 (50.9)	0.4
Initiated ART by 6 months postpartum	16 (25.8)	8 (21.1)	17 (28.8)	0.7

Note: Chi-square test

3-4. Incidence of non-adherence among health facility

The Log-rank test demonstrated incidence of non-adherence was significantly different in the 11 facilities ($p<0.01$) (Table 4). The referral health center, three PHCs with ART services, and one PHC without ART services observed more non-adherence events than expected.

Table 4. Incidence of non-Adherence among 11 Health Facilities.

Facility Number	Subjects	Observed Incidence	Expected Incidence	*p* -value
1	130	189	147.8	**<0.01**
2	33	53	43.6	
3	12	5	18.7	
4	20	41	32.5	
5	23	16	45.2	
6	18	35	25.7	
7	24	25	30.6	
8	7	11	9.2	
9	16	15	21.6	
10	16	14	25.0	
11	22	28	32.1	

Note: Log-rank test

3-5. Probability of remaining adherence by facility type

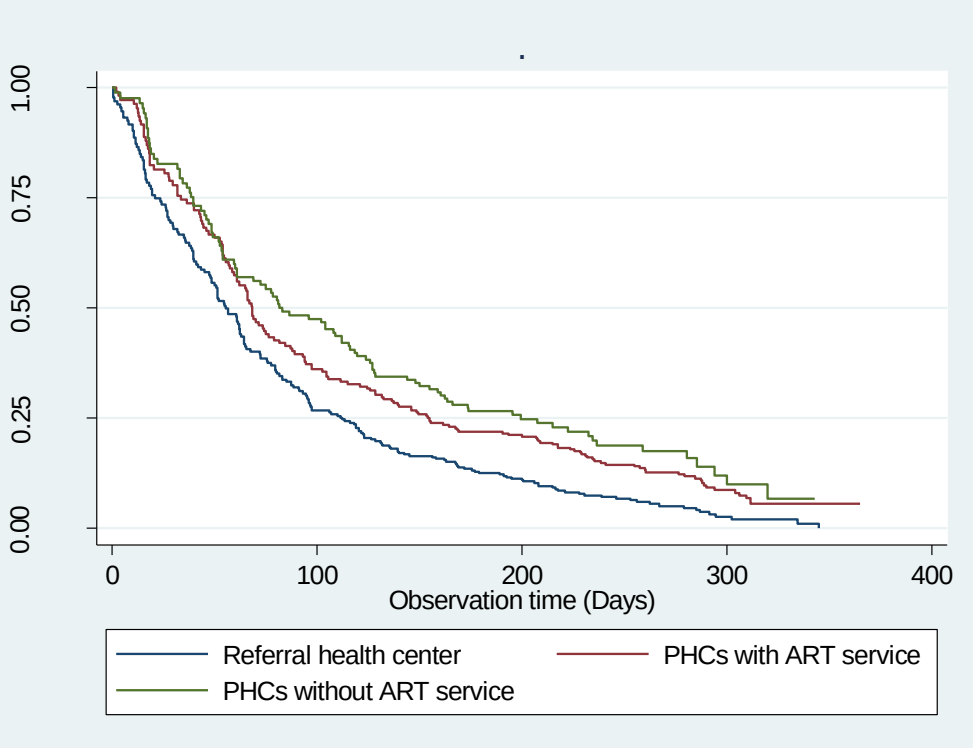
Table 5 describes the probability of remaining adherent, in which midpoint was used for censorship, among the referral health center, five PHCs with ART services, and five PHCs without ART services. Overall probability of adherence in 11 facilities was 0.54 (95% confidence interval (95% CI), 0.49-0.59), 0.30 (95% CI, 0.26-0.34), 0.19 (95%CI, 0.16-0.23), and 0.12 (95% CI, 0.10-0.15) at 60 days, 120 days, 180 days, and 240 days accordingly. In the same way, the probability of adherence was plotted using the Kaplan Meier survival method (Figure 2), which was significantly different in the three facility types (Log-rank test $p<0.01$).

Table 5. Probability of Adherence by Health Facility Type.

Observation time (days)	Overall		Referral Health Center		PHCs with ART service		PHCs without ART service	
	Probability	95%CI	Probability	95%CI	Probability	95%CI	Probability	95%CI
60	0.54	0.49 - 0.59	0.49	0.41 - 0.56	0.57	0.48 - 0.66	0.59	0.48 - 0.68
120	0.30	0.26 - 0.34	0.23	0.17 - 0.29	0.33	0.25 - 0.40	0.39	0.30 - 0.48
180	0.19	0.16 - 0.23	0.13	0.09 - 0.17	0.22	0.16 - 0.28	0.27	0.19 - 0.35
240	0.12	0.10 - 0.15	0.07	0.04 - 0.11	0.15	0.10 - 0.20	0.19	0.12 - 0.27

Note: Kaplan-Meier product limit methods.

Figure 2. Probability of Adherence to ARV by Health Facility Type.



Note: Kaplan-Meier product limit methods.

3-6. Evaluation of the proportional hazard assumption

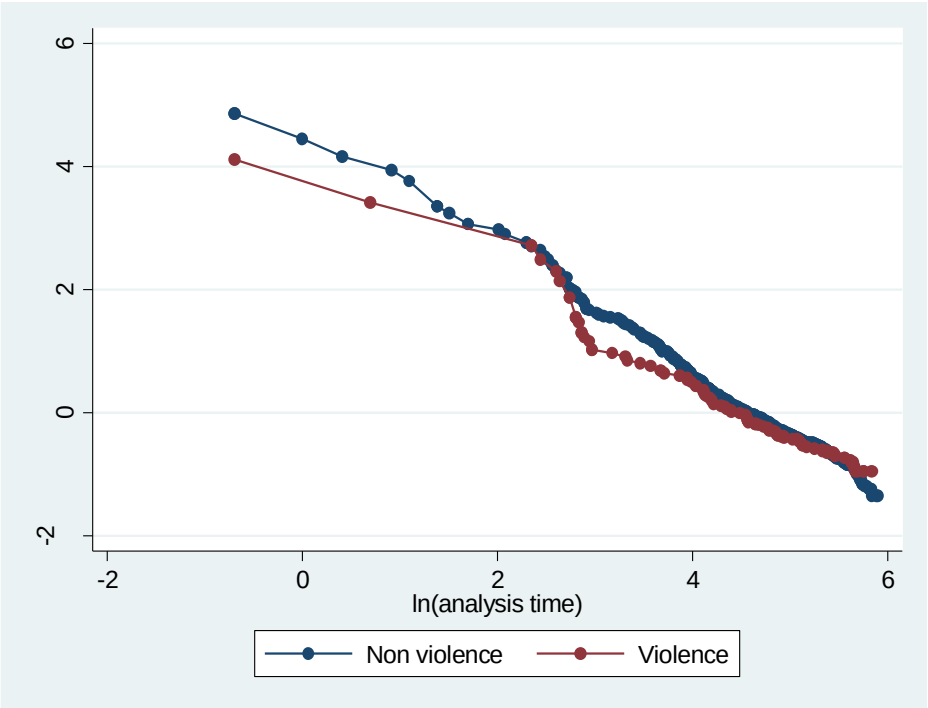
The proportional hazard assumption was evaluated using Schoenfeld residuals, which showed non-significance in a global test (p=0.8), although the domestic violence variable was significant (p=0.04) (Table 6). The log-minus-log survival curve for domestic violence was plotted, but it did not appear to seriously violate the proportional hazard assumption (Figure 3). Overall the model appeared to meet the proportional hazard assumption, and no further adjustments were deemed necessary.

Table 6. The Proportional Hazard Assumptions of All Covariates.

	rho	p-value
Age	-0.04	0.4
Education level	0.04	0.5
Marital status	-0.05	0.3
Primary health centers with ART service	0.01	0.8
Primary health centers without ART service	0.00	1.0
HIV diagnosis	0.00	0.9
ARV regimen	0.05	0.4
Study enrolment	-0.05	0.3
Baseline ARV adherence	-0.01	0.9
Internalized stigma	0.02	0.6
Attitude on taking ARV	0.02	0.7
Had couple HIV testing and counseling	-0.04	0.4
Disclosed HIV status to partner	0.02	0.6
HIV status of partner: Positive	0.02	0.7
HIV status of partner: Unknown	0.01	0.8
Domestic violence	-0.10	0.04
Travel time to health facility	-0.01	0.9
Global test		0.8

Note: Schoenfeld residuals.

Figure 3. The Proportional Hazard Assumption of Domestic Violence.



Note: Log-minus-log survival plot.

3-7. Risk factors for non-ARV adherence in the main model

Table 7 indicates the risk factors for non-ARV adherence in the Cox proportional regression model. As the final model shows, mothers attending the PHCs with ART services (hazard ratio (HR: 0.71, 95% CI: 0.57-0.88) and mothers attending the PHCs without ART services (HR: 0.58, 95% CI: 0.46-0.74) were less likely to be non-adherent to ARV than mothers attending the referral health center. Mothers newly diagnosed as HIV-positive during pregnancy were more likely to be non-adherent than those who already knew their HIV status before pregnancy (HR: 1.24, 95% CI: 1.03-1.50).

Table 7. Risk Factors for non-Adherence to ARV (Main Model)[a].

Variables	Full model[b]			Final model[c]		
	HR	95% CI	p-value	HR	95% CI	p-value
Age						
≤29	1.00			1.00		
≥30	1.00	0.83 - 1.21	1.0	0.99	0.82 - 1.19	0.9
Education level						
≤Primary	1.00			1.00		
≥Secondary	0.95	0.77 - 1.17	0.6	0.91	0.75 - 1.11	0.4
Marital status						
Not married	1.00			1.00		
Married	0.92	0.67 - 1.27	0.6	0.97	0.75 - 1.25	0.8
Facility type						
Referral health center	1.00			1.00		
PHCs with ART service	**0.72**	**0.56 - 0.92**	**<0.01**	**0.71**	**0.57 - 0.88**	**<0.01**
PHCs without ART service	**0.58**	**0.45 - 0.76**	**<0.01**	**0.58**	**0.46 - 0.74**	**<0.01**
HIV diagnosis						
Already diagnosed	1.00			1.00		
Newly diagnosed	1.25	0.98 - 1.61	0.08	**1.24**	**1.03 - 1.50**	**0.03**
ARV regimen						
Prophylaxis	1.00					
Treatment	1.03	0.81 - 1.31	0.8			
Study enrolment						
During pregnancy	1.00					
After delivery	1.12	0.90 - 1.39	0.3			
Baseline ARV adherence						
Adherence	1.00					
Non-adherence	1.13	0.88 - 1.44	0.4			
Internalized stigma						
No	1.00					
Yes	0.87	0.70 - 1.09	0.2			
Attitude on taking ARV						
≤2 items agreed	1.00					
3 items agreed	0.90	0.68 - 1.19	0.5			
Had couple HIV testing and counseling						
No	1.00					
Yes	1.10	0.85 - 1.41	0.5			
Disclosed HIV status to partner						
No	1.00					
Yes	1.13	0.83 - 1.53	0.4			
HIV status of partner						
Negative	1.00					
Positive	1.09	0.80 - 1.47	0.6			
Unknown	1.23	0.89 - 1.70	0.2			
Domestic violence						
No	1.00					
Yes	0.96	0.75 - 1.22	0.7			
Travel time to health facility (minutes)						
≤59	1.00					
≥60	0.99	0.80 - 1.23	0.9			

Note: Cox proportional hazard regression.

[a] Main model: Midpoints between two observations were used for censorship.

[b] Full model: All covariates were included regardless of significant levels.

[c] Final model: Age, education, marital status, facility type, HIV diagnosis, and covariates with significance were retained.

3-8. Sensitivity analysis: effect of time definition

This study utilized two models for censorship. The main model used midpoint between the date of the previous observation and the regular cutoff points of the current observation, and the alternative model used regular cutoff points. A comparison between the main model with all covariates (Table 7) and the alternative model with all covariates (Table 8) shows that health facility type was a significant predictor in both models. The hazard ratio for a new diagnosis of HIV during pregnancy was 1.25 (95% CI: 0.98-1.61) in the main model, whereas in the alternative model it was 1.13 (95% CI: 0.92-1.38). For study enrolment after delivery, the hazard ratio in the main model was 1.12 (95% CI: 0.90-1.39), while in the alternative model it was 1.40 (95% CI: 1.17-1.67). Thus, sensitivity analysis indicated that time definition affected the confidence intervals, but did not make any changes in directions of the hazard ratios.

Table 8. Sensitivity Analysis (Alternative Model)[a].

Variables	Full model[b]			Final model[c]		
	HR	95% CI	p-value	HR	95% CI	p-value
Age						
≤29	1.00			1.00		
≥30	0.99	0.85 - 1.15	0.9	0.99	0.85 - 1.15	0.9
Education level						
≤Primary	1.00			1.00		
≥Secondary	0.90	0.76 - 1.07	0.2	0.88	0.74 - 1.03	0.1
Marital status						
Not married	1.00			1.00		
Married	0.90	0.69 - 1.16	0.4	0.96	0.78 - 1.18	0.7
Facility type						
Referral health center	1.00			1.00		
PHCs with ART service	**0.71**	**0.59 - 0.87**	**<0.01**	**0.73**	**0.62 - 0.86**	**<0.01**
PHCs without ART service	**0.69**	**0.55 - 0.86**	**<0.01**	**0.70**	**0.57 - 0.86**	**<0.01**
HIV diagnosis						
Already diagnosed	1.00			1.00		
Newly diagnosed	1.13	0.92 - 1.38	0.2	1.09	0.93 - 1.28	0.3
ARV regimen						
Prophylaxis	1.00					
Treatment	1.03	0.85 - 1.25	0.8			
Study enrolment						
During pregnancy	1.00			1.00		
After delivery	**1.40**	**1.17 - 1.67**	**<0.01**	**1.40**	**1.17 - 1.68**	**<0.01**
Baseline ARV adherence						
Adherence	1.00					
Non-adherence	1.05	0.88 - 1.26	0.6			
Internalized stigma						
No	1.00					
Yes	0.92	0.77 - 1.09	0.3			
Attitude on taking ARV						
≤2 items agreed	1.00					
3 items agreed	0.93	0.76 - 1.13	0.5			
Had couple HIV testing and counseling						
No	1.00					
Yes	1.07	0.88 - 1.30	0.5			
Disclosed HIV status to partner						
No	1.00					
Yes	1.11	0.87 - 1.42	0.4			
HIV status of partner						
Negative	1.00					
Positive	1.05	0.83 - 1.32	0.7			
Unknown	1.10	0.85 - 1.42	0.5			
Domestic violence						
No	1.00					
Yes	1.08	0.90 - 1.29	0.4			
Travel time to health facility (minutes)						
≤59	1.00					
≥60	1.04	0.87 - 1.24	0.7			

Note: Cox proportional hazard regression.

[a] Sensitivity analysis: Regular cutoff points were used for censorship.

[b] Full model: All covariates were included regardless of significant levels.

[c] Final model: Age, education, marital status, facility type, HIV diagnosis, and covariates with significance were retained.

4: Discussion

4-1. Summary of study findings

This study examined ARV adherence of pregnant women and postnatal mothers until 24 weeks postpartum. Since the Zambian government revised the national PMTCT guidelines (based on Option A of the WHO 2010 guidelines), this study was the first operational evaluation on a longitudinal ARV adherence cohort controlling for the effect of loss to follow-up.

The main finding to emerge was that maternal ARV adherence tremendously declined over the high-risk period for mother-to-child HIV transmission. Although no study has examined longitudinal ARV adherence under the WHO 2010 guidelines, a high incidence rate of non-ARV adherence has been consistently observed in various study settings and assessment periods (58-65, 82-84). As seriously high rates of loss to follow-up hindered optimal uptake of PMTCT programs in other African countries (23, 85-88, 103), so they have also affected non-adherence of mothers in the present study. Maternal ARV adherence was affected by a health facility-specific effect: mothers attending secondary health facility showed poorer ARV adherence than those attending primary health facilities. At the individual level, the first diagnosis of HIV infection was a crucial risk factor for non-adherence.

Toward eliminating HIV transmission, a universal "test and treat" strategy is one potential approach, based on providing therapeutic ART to all HIV-positive individuals soon after diagnosis (104). On the other hand, decentralization of ART services into primary care settings has seen a great impact on patients' survival (105). Both approaches will be adopted in the new PMTCT program – namely, the Option B+

regimen that provides for lifelong ART to all HIV-positive pregnant women (39, 106) (Appendix 2). The Option B+ regimen is expected to be advanced to Option A, as Option A assesses eligibility for ARV regimen based on CD4 counts, whereas most mothers in high HIV burden settings are not able to access CD4 testing facilities (107). The Zambian government has prepared for shifting from Option A to Option B+ at the policy level. Thus, before implementing Option B+, operational challenges should be discussed based on this study's findings.

4-2. Secondary health facility

ARV adherence among mothers attending the referral heath center was substantially poorer than in mothers attending the PHCs. This was affected by high incidence of loss to follow-up in referral health center. The poorer adherence in the referral health facility would attribute to maternal-specific factors or facility-specific factors specific, such as performance of health care providers, and availability of drugs and equipment (77, 108-110).

Of the maternal basic characteristics, educational level, marital status, timing of HIV diagnosis, HIV status of partner, and travel time to health facility were different among health facility type. However, any characteristic other than timing of HIV diagnosis was not associated with non-adherence. Meanwhile, long distance to health facility, and mean and cost of transportation are major barriers to access and retain in the HIV care in the resource limited settings (111-113). In the central health facility, many patients come from remote areas, who would have an especially high risk of being non-adherent and being lost to follow-up – a common pattern observed at the hospital

(85, 112). Although travel time was not a risk factor in this study, it will be important to monitor mothers who come from remote area or who potentially transfer out of the referral health facility, and to link them to further PMTCT services.

Health facility type was strongly associated with maternal adherence even after controlling for the basic characteristics of mothers. This suggests that facility-specific characteristics were independently associated with non-maternal adherence. The referral health center has an affiliated laboratory, daily ART clinic, and district pharmacy. Thus mothers attending the referral health center were less likely to experience running out of drugs, or repeated visiting for further clinical examination, compared with mothers attending PHCs. However, such benefits in the referral health center did not translate to better maternal adherence.

The poor adherence observed in the secondary health facility might stem from the heavy workload placed on health care providers and the weak follow-up system for the PMTCT clients. For example, the referral health center opened its antenatal clinic once a week, and provided health check-ups, group pre-test HIV counseling, HIV testing, and individual post-test HIV counseling to about 20 pregnant women on the day. They then found about four HIV-positive pregnant women, dispensed ARV prophylaxis, and took blood samples for CD4 assessment until late afternoon. PHCs also provided the same antenatal care and PMTCT services once a week, but they had only three to eight pregnant women in a day, and found at most one HIV-positive pregnant woman. The large number of HIV-positive pregnant women attending the referral health center also made it difficult for staff and volunteers to identify mothers lost to follow up and trace them. In addition, the referral health center did not necessarily show better performance in provision of couples HIV testing and counseling, referral of PMTCT

clients to ART clinics, or subsequent ART initiation, compared with PHCs. This indicates that the referral health center had limited capacity to provide essential PMTCT interventions relative to the PHCs due to work burden on staff and volunteer workers.

A study in South Africa reported that increased numbers of new HIV patients per health worker per year were associated with retention in ART services (114). This finding indicates that a higher patient load would detract from communicating with patients and supervising staff (114). This added workload could also limit health workers' ability to provide sufficient counseling (114), leading to lower ARV adherence and treatment interruption. Because of staff shortages, mothers must wait for longer periods of time to receive services, which also affects increased loss to follow-up (115). To improve retention and adherence among mothers attending referral health facilities, potential strategies might be to accelerate decentralization of PMTCT and ART services and minimize the necessity of repeated visits for prescription refilling and health check-ups (85, 112).

Implementation of the Option B+ regimen will promote decentralization of PMTCT services and reduce clients traveling from peripheral areas to the referral health center. However, staff and trained volunteers will also carry an additional workload in dispensing the therapeutic ARV regimen within the PMTCT program. Further task-shifting from clinicians to midwives and nurses, from midwives and nurses to trained volunteers would generate operational challenges. Through steps to careful task-shifting, training and allocating more staff and volunteers, and consistently supervising their performance should be considered (109, 116, 117).

4-3. Primary health facilities

Mothers attending PHCs exhibited a better adherence than mothers attending the referral health center. In contrast to the referral health center, PHCs treated 10 to 30 HIV-positive mothers within a year, which would enable them to provide better PMTCT services and prevent loss to follow-up and treatment interruption. During the observation period, trained TBAs who worked as interviewers for the present research were key players in connecting PMTCT services between health facilities and the community. They engaged in providing HIV testing, ARV prophylaxis, and adherence counseling at the health facilities, while also accompanying mothers to health facilities for delivery and advising them to receive postnatal ARV prophylaxis if mothers delivered at home. They also educated mothers on exclusive breastfeeding along with the benefits of taking ARV prophylaxis. However, these staff did not perform such function in the referral health center.

Continuous support by trained volunteers beyond facility is beneficial for HIV-positive mothers as they were a high-risk population for loss to follow-up and interruption of ARVs. In Malawi, trained community health workers have functioned as coordinators, improved retention, and increased utilization of PMTCT services (118). In addition, they can work for protect maternal and child health. A study in South Africa reported that 25% of child death was avoidable if family or community members detected sick children and referred them to health services effectively (119). Although trained volunteers such as TBAs have complemented staff shortages in the PMTCT program in other parts of sub-Saharan Africa, standardizing their knowledge and skills through regular training and supervision, and evaluating their performance will be important to utilizing this workforce effectively for better PMTCT services (120-123).

The Option B+ approach will be applied in Zambia from 2013. In accordance with the implementation of Option B+ in Malawi since 2011, all health facilities with antenatal clinic have integrated ART services into the PMTCT program (124). Within a year from introducing the Option B+, ART was successfully initiated among seven times more pregnant women and lactating mothers at a retention rate of 77% - a similar level to adults initiating ART during the period (124). An intervention study conducted in Zambia also reported that providing ART services at antenatal clinics increased the number of pregnant women who initiated ART before giving birth (125). In Zambia, however, only 25% of health facilities offered ART services for general HIV patients and 25% provided virological HIV testing to HIV-exposed children (42). Similarly, of the 19 PHCs in the study site, only five PHCs offered both PMTCT and ART services. Limited availability of ART services requires additional access to health facilities for HIV-positive mothers to continue lifelong ART. Even though the more efficacious ARV regimen is provided in Option B+, such limited availability of ART services would increase the risk of loss to follow-up and treatment interruption. Thus, preparations should be made toward expanding ART services to all PHCs simultaneously.

4-4. Newly diagnosed and ARV naïve mothers

Mothers newly diagnosed as HIV-positive were at higher risk of non-adherence than mothers who already knew their HIV status before pregnancy. Several previous studies support this finding. In the United States, mothers initiating ART before pregnancy showed better adherence (59), two studies in sub-Saharan Africa also

reported that mothers on ART were more likely to administer sd-NVP to their infants within 72 hours (71), and less likely to miss ARV at labor and delivery (74).

Opt-out HIV testing for pregnant women has made a great contribution to detect new HIV-positive women (22). However, few studies have discussed the risks for non-adherence and attrition following the first diagnosis of HIV infection. In contrast to the mothers who already knew their HIV status, newly diagnosed HIV-positive mothers must deal with various novel issues after receiving HIV diagnosis, including the shock of diagnosis with a permanent and potentially fatal disease, disclosure of HIV status to their spouses, the new daily routine of medication, side-effects of ARV (e.g. AZT-related anemia) (91), and the need for access to HIV care and treatment services. Poor physical and mental health and stigmatization are likely to make such issues more complicated (123).

Universal HIV test and treatment before pregnancy can potentially improve PTMCT strategies by reducing the risk that pregnant women are not aware of their HIV status, thus it can reduce the number of women who suffer from complications attributed to new HIV diagnosis-related. This approach will be also beneficial to primary prevention among the reproductive aged population, which is highlighted as one of the four targets in the PMTCT program (21). Despite the high HIV prevalence in the study site, half of the participant mothers did not notice their HIV-positive status until antenatal HIV testing, and 40% of their partners remained of unknown status. This is a common situation across the country, in which about 70% of HIV-positive men and 50% of HIV-positive women had never been tested before their first HIV-positive diagnosis (48). Thus, improving the rate of testing in the community and encouraging regular testing among all sexually active young people will likely have subsidiary

benefits for PMTCT strategies, as it will reduce the number of women who are unprepared for initiation of ARV in pregnancy. PHCs and other health agencies in Zambia should redouble their efforts to encourage HIV testing in the general population, and novel approaches should be found to encourage those considering starting a family, or those in stable sexual relationships, to obtain regular HIV testing. Additionally, cost-effectiveness of this strategy should be evaluated, as it requires considerable financial investment and human resource (126).

Corresponding to HIV testing before pregnancy approach, couple testing and counseling will be also an effective intervention to improve adherence of mothers newly diagnosed as HIV positive. Previous studies have demonstrated its multiple effects, such as promoting disclosure of HIV status among couples (47, 127), reducing loss to follow-up (80), increasing provision of ARV prophylaxis (128) and administration of ARV (129, 130) with no association with domestic violence and abuse attributed to disclosing HIV status to partner (95). Thus, couple HIV testing and counseling will provide various benefits to improve uptake of PMTCT program in women newly diagnosed as HIV-positive and their partners. However, only 40% of the study participants have taken couple HIV testing and counseling. A future research should focus on individual- and facility-specific barriers to expand the couple HIV testing and counseling service in the study site.

Further efforts for enrolment in the ART clinic is also needed to improve adherence in newly diagnosed HIV-positive mothers. As previous studies reported, better adherence of mothers already on ART was a consequence of longer experience of medication and improved health status by taking ARV, stronger risk perception for the disease, and increased opportunities for adherence support (59, 71). In contrast, newly

diagnosed HIV-positive mothers are ARV naïve and have less directly experienced HIV-related symptoms (131). Lack of information on ART services and negative perception on ARV drugs were also barriers to start or continue ART (132). Initially, HIV-positive mothers have a strong intention to protect and take care of their children, and such motivation facilitates their adherence (84, 133, 134). Despite this, 30% of maternal death was caused by HIV-related disease in 2010 in Zambia (135). Thus, it is crucial to develop knowledge of health risks and available health services to establish better compliance with prescribed drugs (136-138). ART clinics play a crucial role in providing such information through clinical examination, treatment, and adherence counseling that cannot be covered in the PMTCT program. Although the primary determinant of whether HIV-positive mothers access HIV treatment is their personal health-seeking behavior, the PMTCT program needs to make further effort to ensure referrals of the mothers to ART clinics.

4-5. Limitations

Although this study yielded novel findings toward improving the PMTCT services in Zambia and comparable settings, it has several limitations. First, this study used a single measurement of self-reported ARV adherence. Any self-reported measurement is potentially affected by recall bias and social desirability bias. However, a four day self-report adherence instruments asked the latest adherence, to maximize recall while minimize bias (92). Thus it was unlikely to be much affected by recall bias.

Second, this study might overestimate incidence of non-adherence because all subjects who did not attend scheduled interviews were treated as non-adherent.

However, it would be rational to consider that mothers missed the scheduled visits were likely to be non-adherence to medication (100). In addition, this is an operational research using intention-to-treat analysis, designed to observe the standard practice of the PMTCT program and give conservative results. It would be worthwhile to conduct an intervention study to trace mothers who missed interviews and who were lost to follow up, and investigate their reasons and ARV adherence while lost to follow-up.

Third, detailed information on facility characteristics was not collected in the study, although health facility type was a predictor for adherence. Further study is warranted to collect additional data about facility-specific characteristics that would facilitate or hinder adherence with the PMTCT program.

Despite these limitations, the study constitutes a significant contribution to the field in operating the 2010 PMTCT guidelines, as it identified risk factors for ARV non-adherence in a longitudinal cohort, controlling for the effects of loss to follow-up that have seriously undermined the program outcomes. Based on the findings, potential operational challenges toward implementing the advanced protocol of Option B+ were indicated.

5: Conclusions and Recommendations

This is the first prospective cohort study that assessed ARV adherence in the PMTCT program since the Zambian government introduced an extended prophylaxis regimen based on WHO 2010 guidelines. High incidence of non-adherence was observed by controlling for the effect of loss to follow-up.

Mothers attending a referral health center showed poorer adherence than mothers attending PHCs. The Zambian government plans to adopt the Option B+ regimen, which offers lifelong ART to all HIV-positive pregnant women and postnatal mothers. Based on the study findings, several interventions are recommended to operate the Option B+ effectively. In the referral health center, the Option B+ regimen will increase staff workload due to treating the largest number of PMTCT clients. This will further affect maternal retention and adherence in the PMTCT program. Although a future goal should be to provide PMTCT services by skilled health workers, increasing trained TBAs and careful task-shifting, and continuous follow-up beyond health facility are crucial responses to improve the quality of the services and retention of clients in the referral health center. In the PHCs, on the other hand, general ART services should be expanded to all sites in conjunction with the PMTCT program. Otherwise, loss to follow-up and treatment interruption will undermine the program outcome.

New HIV diagnosis during pregnancy was a significant risk factor for non-adherence due to multiple issues following the HIV diagnosis. Opt-out antenatal HIV testing is an effective intervention to detect new HIV cases in pregnant women. However, expanding HIV testing and treatment before pregnancy will also help women to overcome multiple barriers to medication in advance, and to improve their adherence

and retention in the program. In addition, scale up of couple HIV testing and counseling, and integrated ART services in the PMTCT program will be also beneficial for mothers newly diagnosed as HIV-positive to improve their adherence. Health centers, international organizations operating in Zambia, and the Zambian health authorities should redouble their efforts to improve testing rates among sexually active young people and to encourage regular testing even among women in stable relationships. Such a program will have benefits not only in general HIV prevention, but in improving the effectiveness of PMTCT programs through reducing the number of women entering antenatal care who are naïve to their own HIV status.

Towards eliminating mother-to-child transmission of HIV and keeping HIV-positive mothers survival longer, not only prescribing efficacious ARV regimen, but comprehensive services to reduce loss to follow-up and improve adherence is necessary, considering both facility- and individual-specific factors. Simultaneously, cost-effectiveness in the PMTCT program should be taken into account as it requires huge financial investment. Through such tactics, Zambia can improve both the health of pregnant women with HIV and their babies, and also minimize the risk of HIV transmission to a new generation, and make a significant contribution to the long-term eradication of this epidemic.

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Appendices

Appendix 1. Major Revisions in the WHO Guidelines from 2006 to 2010 Option A.

2006 guidelines	2010 guidelines
[1] ARV eligibility criteria	
▸Clinical stage 1-2 with CD4 < 200 cells/mm^3 ▸Clinical stage 4, irrespective of CD4 cell count ▸Clinical stage 3, with CD4 < 350 cells/mm^3	▸CD4 ≤ 350 cells/mm^3, irrespective of clinical stage ▸Clinical stage 3-4, irrespective of CD4 cell count
[2] Timing to start ARV prophylaxis	
▸From 28 weeks of gestation	▸As early as 14 weeks of gestation
[3] Prophylaxis regimen for HIV-exposed infants	
(i) Infants born to mothers on ART	
▸zidovudine (AZT) for 7 days	▸nevirapine (NVP) or AZT for 4-6 weeks
(ii-a) Breastfeeding infants born to mothers not on ART	
▸single-dose NVP + AZT for 7 days	NVP from birth to until 1 week after complete cessation of breastfeeding
(ii-b) Non-breastfeeding infants born to mothers not on ART	
▸single-dose NVP + AZT for 7 days	NVP or single-dose NVP + AZT for 4-6 weeks

Modified from Antiretroviral drugs for treating pregnant women and preventing HIV infections in infants: recommendations for a public health approach 2010 version (WHO).

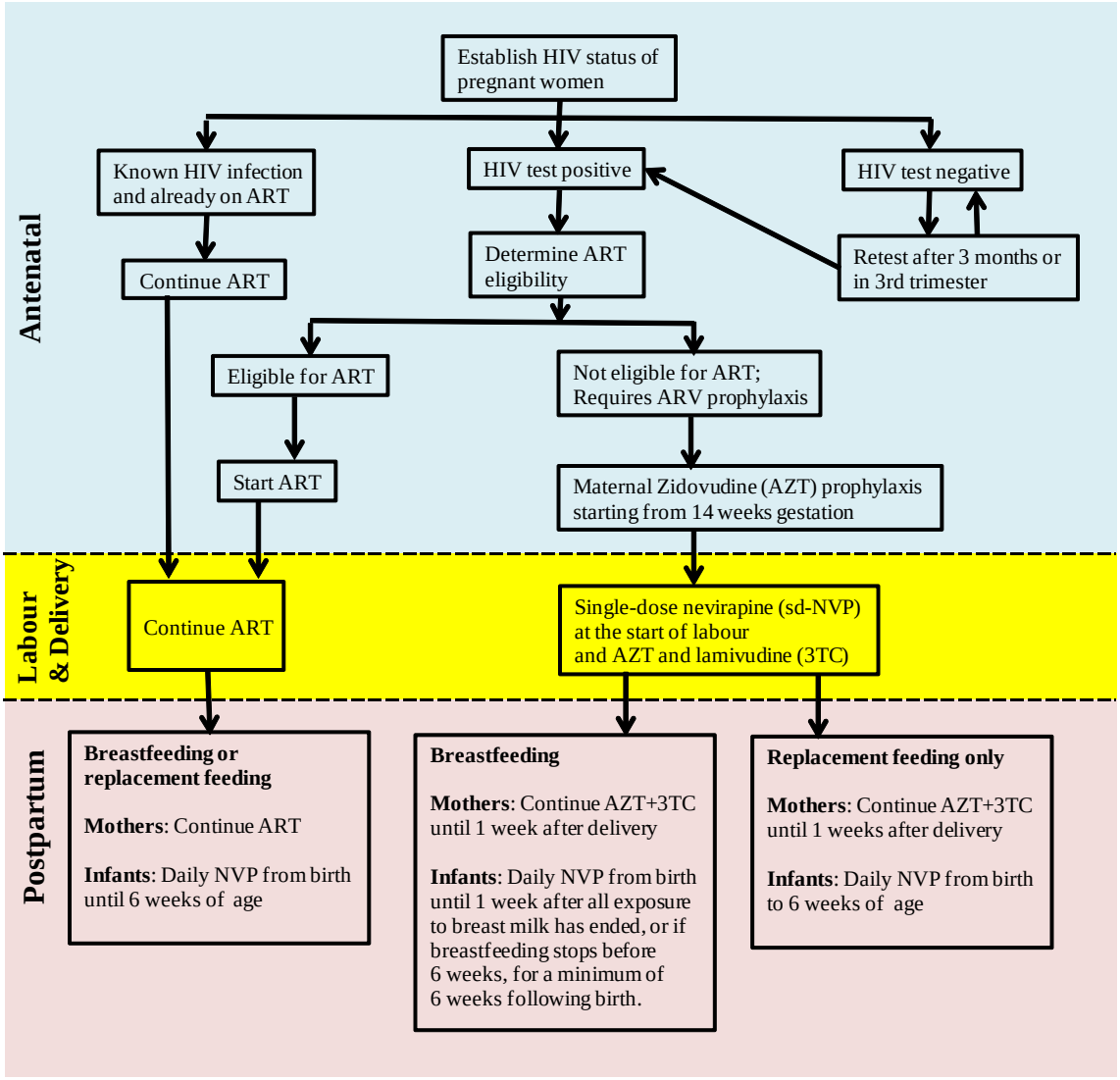
Appendix2. Three Options of WHO PMTCT Guidelines.

	Mother: Treatment (CD4 count ≤ 350 cells/mm^3)	**Mother: Prophylaxis** (CD4 count > 350 cells/mm^3)	**Infant**
Option A	Triple ARVs initiation soon after diagnosis, and continued for a lifelong.	***Antepartum*** : AZT[a] starting from 14 weeks of gestation ***Intrapartum*** : At onset of labor, single-dose NVP[b] and AZT/3TC[c] administering ***Postpartum*** : Daily AZT/3TC for 7 days postpartum taking	If infant on breast feeding, daily NVP from birth to 1 weeks after complete cessation of breastfeeding; or if infant not on breastfeeding or if mother on ART, daily NVP from birth to 4-6 weeks
Option B	Triple ARVs starting soon after HIV diagnosis, and continued for a lifelong	Triple ARVs starting from 14 weeks of pregnancy and continued until delivery if infant not on breastfeeding; or continued by mother until 1 week after complete cessation of breastfeeding	All infants ingest daily NVP or AZT from birth to 4-6 weeks
Option B+	Triple ARVs starting as soon as diagnosis, continued for a lifelong	Triple ARVs starting as soon as diagnosis, continued for a lifelong	All infants take daily NVP or AZT from birth to 4-6 weeks

Modified from Programmatic update: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants executive summary (WHO).

[a]zidovudine, [b]nevirapine, [c]lamivudine.

Appendix 3. 2010 Zambia National Protocol Guidelines



Modified from 2010 National Protocol Guidelines. (Ministry of Health, Republic of Zambia)

Appendix 4. Literature Review on Risk Factors of non-Adherence.

Study	Year	Country	Stage / Subject	Adherence	Risk factor
[1] High-income country					
Laine[59]†	2000	USA	antenatal	34%	not used ART before pregnancy, ethnicity(Black, Hispanic), age<20, residence area (New York)
Wilson[60]	2001	USA	antenatal	80%	illicit drug use, missed prenatal vitamin
Demas[61]	2002	USA	neonatal	71%	poor social support network, not disclosed HIV status, poor antenatal adherence, asymptomatic status, have >2 children
Ickovics[62]	2002	USA	antenatal	50%‡	administered >2 times/day
			postnatal	34%‡	
Demas[63]	2005	USA	antenatal	68%	not disclosed HIV status, not participated in support group
Bardeguez[64]	2008	USA	antenatal	75%	used ART before pregnancy, had AIDS, missed prenatal vitamin, used marijuana, not felt happy
			postnatal	64-66%	
Mellins[65]	2008	USA	antenatal	61%	higher viral load, HIV symptoms, clinic attendance>6 times, alcohol consumption
			postnatal	44%	
[2] Sub-Saharan Africa, intrapartum nevirapine regimen					
Stringer[78]	2003	**Zambia**	mother (intervention)	61%	intervention arm (offered NVP without HIV testing), illiteracy, non experience of prior fetal or infant death
			mother (control)	74%	
Stringer[66]	2005	**Zambia**	mother	68%	longer interval between HIV test and delivery
			infant	90%	
Albrecht[67]	2006	**Zambia**	mother	94%	home delivery, no high school education, low newborn birth weight
			infant	91%	hospital delivery, low apgar score, infant death within 28 days of age
Karcher[68]	2006	Tanzania	mother	42%	self-administered NVP at home, age<25, non-secondary education, non-Catholic religion, not had PMTCT counseling at hospital
			infant	44%	
		Uganda	mother	46%	
			infant	24%	
Bii[69]	2007	Kenya	mother	90%	antenatal attendance<2, age<20, single woman, home delivery, maternal poor adherence
			infant	91%	
Kasenga[76]	2007	Malawi	mother	75%	home delivery
			infant	52%	
Chi[79]	2008	**Zambia**	mother	54%	(not reported)

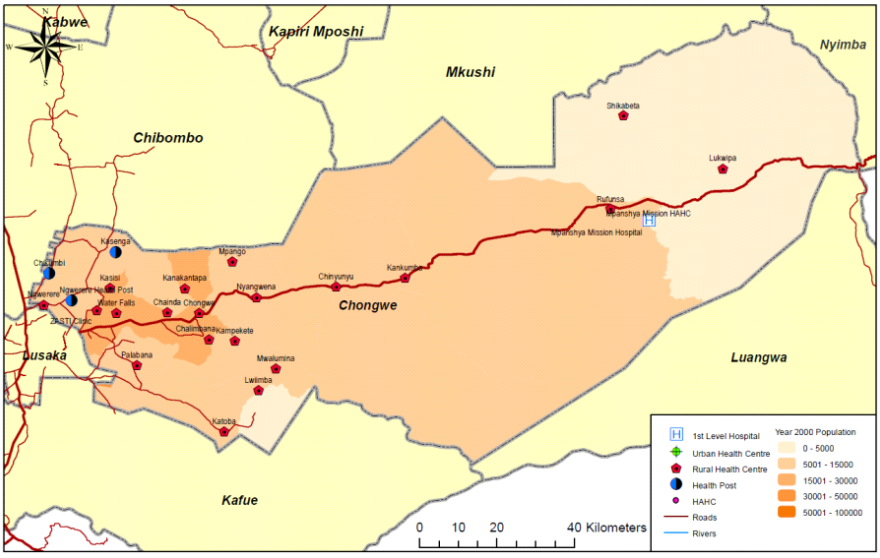
Delvaux[70]	2009	Rwanda	mother-infant	53%	unmarried, education<3 years, antenatal attendance <2, offered HIV test after first antenatal attendance, not disclosed HIV status
Barigye[71]	2010	Uganda	mother	60%	residence area (not study site), first antenatal attendance at early pregnancy, preferred to receiving NVP at facility, 24<age>35, not on ART
			infant	43%	
Conkling[80]	2010	**Zambia**	mother	79%	(no significant factor)
		Rwanda	mother	88%	
Kuonza[72]	2010	Zimbabwe	mother	69%	not experienced PMTCT program, not prescribed NVP in advance, no secondary education, multi-parity, home delivery, not disclosed HIV status
			infant	73%	
Megazzini[81]	2010	**Zambia**	mother-infant (intervention)	52%	control arm (vs. intervention arm: offered HIV test after HIV test and NVP adherence assessment at labor ward)
			mother-infant (control)	43%	
Peltzer[73]	2010	South Africa	mother	78%	poor knowledge of PMTCT, not disclosed HIV status, premature delivery, not told partner about HIV test or ARV, not knew infant's HIV status
			infant	77%	
Stringer[74]	2010	Cameroon	mother	85%	age<30, gravidity>4, antenatal attendance<6, vaginal delivery, single dose NVP regimen (vs. ART)
		Cote d'Ivoire		69%	
		South Africa		82%	
		Zambia		79%	
Mirkuzie[75]	2011	Ethiopia	mother	60%	home delivery
			infant	87%	
[3] Sub-Saharan Africa, ARV prophylaxis regimen					
Chung[57]	2008	Kenya	antenatal-postnatal	96%‡	not reported
Kirsten[58]	2011	Tanzania	antenatal	50%	age<24, no income generating activity, enrolled in PMTCT<24week, not disclosed HIV status
			intrapartum mother	42%	
			postnatal infant	19%	
Peltzer[82]	2011	South Africa	antenatal	61%	not disclosed HIV status, discrimination, poor partner involvement
			postnatal	86%	
Mepham[83]	2011	South Africa	antenatal-postnatal	61%	qualitative answer: misunderstood therapy, domestic violence, poverty, not disclosed HIV status, stigma
Ekama[84]	2012	Nigeria	antenatal	81%	not disclose HIV status, not have treatment partner

† reference number

‡ mean level of adherence

Appendix 5. Maps of Study Site.

Chongwe District/ Lusaka Province



Appendix 6. Survey Tools

1.Basic Information

1 Research ID — Facility ☐☐ – Participant ☐☐☐

* Facility code		
01. Chongwe	04. Chinyunyu	08. Chitemalesa
02. Kanakantapa	05. Kasisi	09. Kampekete
03. Chalimbana	06. Lwiimba	10. Mpango
	07. Chainda	11. Nyangwena

2 Date of Enrolment (DD/MM/YYYY) ☐☐ – ☐☐ – ☐☐☐☐

3 Safe Motherhood No. ☐☐☐☐ – ☐☐☐ – ☐☐☐☐☐ – ☐☐

4 Under five No. ☐☐☐☐ – ☐☐☐ – ☐☐☐☐☐ – ☐☐

*If twin, under five No. of the second baby

☐☐☐☐ – ☐☐☐ – ☐☐☐☐☐ – ☐☐

5 Name of ART clinic

6 Age

7 Participant's Date of Birth (DD/MM/YYYY) ☐☐ – ☐☐ – ☐☐☐☐

8 Baby's Date of Birth (DD/MM/YYYY) ☐☐ – ☐☐ – ☐☐☐☐

9 Language of the interview

English	Nyanja	Bemba	Tonga	Other ( )
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

2.Register Data

Research ID _____

1 Antenatal Details (1:Antenatal Card, 2:Safe motherhood Register, 3:Integrated Counselling Register)

1	Date of 1st antenatal visit (2-a)		(dd/mm/yyyy)		☐ No Record
2	Last menstruation period [LMP](2-i)		(dd/mm/yyyy)		☐ No Record
3	Gestation in week at 1st ANC(2-k)		weeks		☐ No Record
4	Estimated delivery date [EDD](2-j)		(dd/mm/yyyy)		☐ No Record
5	Gravida (2-g)		times		☐ No Record
6	Parity (2-h)		times		☐ No Record
7	Syphilis test (2-s.t)	RPR 1	Reactive ☐ 1	Negative ☐ 0	☐ No Record
		RPR 2	Reactive ☐ 1	Negative ☐ 0	☐ No Record
8	Syphilis treatment (2)		Treated ☐ 1	Not treated ☐ 0	☐ No Record
9	Total number of ANC visits (2-a)		times		☐ No Record
10	Partner took HIV test (3-i)	Tested	Yes ☐ 1	No ☐ 0	☐ No Record
		Date	(dd/mm/yyyy)		☐ No Record
		Result	Positive ☐ 1	Negative ☐ 0	☐ No Record

2 Delivery Details (1:Antenatal Card, 2:Delivery Register, 3:MTCT Labour Ward Register)

1	Date of Delivery (1, 2 or 3)	Date(dd/mm/yyyy)			☐ No Record
		Gestation ( ) week			☐ No Record
2	Outcome of delivery (3-o)	Alive ☐ 1	Died ☐ 0		☐ No Record
3	Apgar score (2-ad)	( ) / (10 scores)			☐ No Record
4	Birth weight (2-ae)	( ) days of age	( ) kg		☐ No Record
5	Sex of baby (2-ag)	Female ☐ 1	Male ☐ 0		☐ No Record
6	Place of delivery (2)	Home ☐ 1 Facility( ) ☐ 2 Other( ) ☐ 3			☐ No Record
7	Mode of Delivery [MoD] (2-u)	Vaginal ☐ 1	Caesarean ☐ 0		☐ No Record
8	Place NVP was taken at labour (3-k&l)	Did not take ☐ 0 Took at Home ☐ 1 Took at Facility ☐ 2		☐ On ART	☐ No Record
9	Intrapartum AZT & 3TC (3-m)	Taken ☐ 1	Not taken ☐ 0	☐ On ART	☐ No Record
10	7 days Postnatal AZT& 3TC to mother	Given ☐ 1	Not given ☐ 0	☐ On ART	☐ No Record
11	ARV prophylaxis to Baby (3-n)	Given ☐ 1	Not given ☐ 0		☐ No Record

2.Register Data

Research ID _____

3 Postnatal Details (1:Children under 5 card, 2:Children under 5 register)

1	Date of 6 days visit		(dd/mm/yyyy)	☐ No visit	☐ No Record
2	Date of 6 weeks visit		(dd/mm/yyyy)	☐ No visit	☐ No Record
3	Immunization	1) BCG (2-g)	Given ☐ 1	Not given ☐ 0	☐ No Record
		2) BCG scar (2-h)	Given ☐ 1	Not given ☐ 0	☐ No Record
		3) DPT/HepB/Hib-1(2-i)	Given ☐ 1	Not given ☐ 0	☐ No Record
		4) DPT/HepB/Hib-2(2-j)	Given ☐ 1	Not given ☐ 0	☐ No Record
		5) DPT/HepB/Hib-3(2-k)	Given ☐ 1	Not given ☐ 0	☐ No Record
		6) OPV-0 (2-l)	Given ☐ 1	Not given ☐ 0	☐ No Record
		7) OPV-1(2-m)	Given ☐ 1	Not given ☐ 0	☐ No Record
		8) OPV-2(2-n)	Given ☐ 1	Not given ☐ 0	☐ No Record
		9) OPV-3(2-o)	Given ☐ 1	Not given ☐ 0	☐ No Record
		10) OPV-4(2-p)	Given ☐ 1	Not given ☐ 0	☐ No Record
		11) Measles (2-q)	Given ☐ 1	Not given ☐ 0	☐ No Record
4	Vitamin A supplement	1st (2-aa)	Given ☐ 1	Not given ☐ 0	☐ No Record
		2nd(2-ag)	Given ☐ 1	Not given ☐ 0	☐ No Record
		3rd(2-ak)	Given ☐ 1	Not given ☐ 0	☐ No Record

4 Mother ARV Prophylaxis/ ART Details (1:Integrated Counselling Register, 2:ART patient file, 3:SmartCare)

1	Date of HIV diagnosis(1-B or L, 2 or 3)	(dd/mm/yyyy)	☐ No Record
2	Date of Prophylaxis AZT initiated (1-remarks)	(dd/mm/yyyy)	☐ No Record
3	Date of Cotrimoxazole initiated (1-remarks)	(dd/mm/yyyy)	☐ No Record
4	Date of referral to ART clinic (1-q)	(dd/mm/yyyy)	☐ No Record
5	Date of enrolment in Pre-ART clinic(2or3)	(dd/mm/yyyy)	☐ No Record
6	Pre-ART Number(2or3)		☐ No Record
7	Date of enrolment in ART clinic(2or3)	(dd/mm/yyyy)	☐ No Record
8	ART Number(2or3) ☐☐☐☐ - ☐☐☐ - ☐☐☐☐☐ - ☐		☐ No Record
9	Date of HAART initiated(2or3)	(dd/mm/yyyy)	☐ No Record

2.Register Data **Research ID** _____

5 Infant ARV Prophylaxis/ ART Details (1:Baby Mother Follow up Register, 2:ART patient file, 3:SmartCare)

1 Date of Prophylaxis NVP initiated(1-u)	(dd/mm/yyyy)	☐ No Record
2 Date of Cotrimoxazole initiated(1-u)	(dd/mm/yyyy)	☐ No Record
3 Date of HIV diagnosis(1-s,t, ad,ae)	(dd/mm/yyyy)	☐ No Record
4 Date of referral to ART clinic	(dd/mm/yyyy)	☐ No Record
5 Date of enrolment in ART clinic(2or3)	(dd/mm/yyyy)	☐ No Record
6 ART Number (2or3) ☐☐☐☐ - ☐☐☐ - ☐☐☐☐☐ - ☐		☐ No Record
7 Date of HAART initiated(2or3)	(dd/mm/yyyy)	☐ No Record

6 Survival Status: If mother or baby die or terminated the current pregnancy (abortion), record below and consultant DHO for continuation of study.

1 Date of Mother's death	(dd/mm/yyyy)		☐ No Record
2 Cause of Mother's death			☐ No Record
3 Date of Baby's death	(dd/mm/yyyy)		☐ No Record
4 Cause of Baby's death			☐ No Record
5 Date of Abortion (terminated pregnancy)	(dd/mm/yyyy)		☐ No Record
6 Cause of Abortion	Induced ☐ 1	Natural ☐ 0	☐ No Record

2.Register Data

Research ID _____

7 Mother PMTCT follow up

** If there is no record, please write "NR" in the blank.*

			Antenatal period	6 days after delivery	6 weeks after delivery	6 months after delivery	12 months after delivery	18 months after delivery
1	Height (cm)							
2	Weight (kg)		at enrolment					
3	Haemoglobin (mg/dl)							
4	WHO clinical stage							
5	CD4 assessment	Date(dd/mm/yyyy)						
		CD4 count						
6	Eligibility for ART		Yes ☐ 1 / No ☐ 0	Yes ☐ 1 / No ☐ 0	Yes ☐ 1 / No ☐ 0	Yes ☐ 1 / No ☐ 0	Yes ☐ 1 / No ☐ 0	Yes ☐ 1 / No ☐ 0
7	ARV regimen	Name of Drug1						
		Name of Drug2						
		Name of Drug3						
8	ART refill visits in the last 6 months							

2.Register Data

Mother's Research ID

8 Baby PMTCT follow up

** If there is no record, please write "NR" in the blank.*

			6 days after delivery	6 weeks after delivery	6 months after delivery	12 months after delivery	18 months after delivery
1	Opts for Exclusive Breast feeding(EBF)		EBF ☐ 1 / No ☐ 0	EBF ☐ 1 / No ☐ 0	EBF ☐ 1 / No ☐ 0	EBF ☐ 1 / No ☐ 0	EBF ☐ 1 / No ☐ 0
2	HIV test	Date(dd/mm/yyyy)					
	6wk, 6mo=DBS	Result	R ☐ 1 / NR ☐ 0	R ☐ 1 / NR ☐ 0	R ☐ 1 / NR ☐ 0	R ☐ 1 / NR ☐ 0	R ☐ 1 / NR ☐ 0
	12m,18m=Rapid Test	R= Reactive, NR=Non Reactive	Indeterminate ☐ 2	Indeterminate ☐ 2	Indeterminate ☐ 2	Indeterminate ☐ 2	Indeterminate ☐ 2
3	Height (cm)						
4	Weight (kg)						
5	Haemoglobin (mg/dl)						
6	WHO clinical stage						
7	CD4 assessment	Date(dd/mm/yyyy)					
		CD4 Count					
		CD4 (%)	%	%	%	%	%
8	Eligibility for ART		Yes ☐ 1 / No ☐ 0	Yes ☐ 1 / No ☐ 0	Yes ☐ 1 / No ☐ 0	Yes ☐ 1 / No ☐ 0	Yes ☐ 1 / No ☐ 0
9	ARV regimen	Name of Drug1					
		Name of Drug2					
		Name of Drug3					
10	ART refill visits in the last 6 months						

Enrolment

1 Research ID (Facility) – (Participant)

* Facility code	04. Chinyunyu	08. Chitemalesa
01. Chongwe	05. Kasisi	09. Kampekete
02. Kanakantapa	06. Lwiimba	10. Mpango
03. Chalimbana	07. Chainda	11. Nyangwena

2 Date of Interview (DD/MM/YYYY) ☐☐ – ☐☐ – ☐☐☐☐

3 Safe Motherhood No. ☐☐☐☐ – ☐☐☐ – ☐☐☐☐☐ – ☐☐

S. Confirmation of Study Participant:

Let us confirm whether you are eligible for joining the study.

S002. Did you already known your HIV positive status before the present pregnancy?

Before the pregnancy	☐ 1	
During or After the pregnancy	☐ 0	→ **Go to A009**

S003. Are you already on lifelong treatment for HIV (ART/HAART) before the present pregnancy ?

Yes	☐ 1	
No	☐ 0	→ **Go to A009**

S004. If you are on lifelong treatment (ART), when did you start ART? (dd/mm/yyyy)

S005. Do you visit the same health centre for antenatal clinic and ART clinic?

Same	☐ 1	→ **Go to A009**
Different	☐ 0	
N/A	☐ 99	→ **Go to A009**

S006. Name of health facility for ART clinic :

Before starting, fill in 1) Participant List, 2) Appointment card 3) Basic Information, and 4) Register Data sheet.

A. Socio-demographic Characteristics:

Please answer about your social background.

A009. Age ____ years old

A010. Religion

Christian	Muslim	Other	Nothing
☐ 1	☐ 2	☐ 3	☐ 0

A011. Education level *[the last grade achieved]*

None	☐ 0	
Highest Grade(1-12)	( )	←**Write Grade**
College/University	☐ 13	

A012. Education level of **<u>your partner</u>**
[the last grade achieved]

None	☐ 0	
Highest Grade(1-12)	( )	←**Write Grade**
College/University	☐ 13	
If no partner, N/A	☐ 98	
Don't know	☐ 99	

A013. Number of family members living together including yourself

	Adults
Children (age <18)	

A014. Does anyone in your household own agricultural field?

Yes ☐ 1	No ☐ 0

A015. Do you have the following things in your house?
(Ask one by one)

1)	Tap water	Yes ☐ 1	No ☐ 0
2)	Electricity	Yes ☐ 1	No ☐ 0
3)	Gas/Electricity for cook	Yes ☐ 1	No ☐ 0
4)	Television	Yes ☐ 1	No ☐ 0
5)	Radio	Yes ☐ 1	No ☐ 0
6)	Mobile phone	Yes ☐ 1	No ☐ 0

Please answer about access to the health centre.

A016. How did you come here today?

1)	On foot ☐ 1
2)	Bicycle ☐ 2
3)	Motor bike ☐ 3
4)	Mini bus ☐ 4
5)	Other ( )

A017. How long do you take to travel back to your home? (One way)

hours	minutes

A018. How much does it cost you for travelling back to your home?
One way by means answered in A016.
Ex) If on foot, write Zero.

Kwacha

A019. Is this health centre the closest one to your home?

Yes ☐ 1	No ☐ 0

M. Family Planning:

Please answer about various ways or methods that a couple can use to delay or avoid a pregnancy.

M001. Do you want to have more children?

No	☐ 0
Yes	☐ 1
Declined to answer	☐ 99

M007. Is the current pregnancy/baby planned one?

No	☐ 0	
Yes	☐ 1	→ **Go to another questionnaire.**
Declined to answer	☐ 99	

M003. Did you use any methods to delay or avoid this pregnancy?

No	☐ 0	
Yes	☐ 1	→ **Go to another questionnaire.**
Declined to answer	☐ 99	

M005. ***If No***, why didn't you use <u>any method to delay or avoid a pregnancy (=FP)</u>?
(Ask one by one)

1)	You didn't know any FP method.	Yes ☐ 1	No ☐ 0	**Go to another questionnaire.**
2)	You did not know where you can get a FP method.	Yes ☐ 1	No ☐ 0	
3)	You did not ask health worker for a FP method.	Yes ☐ 1	No ☐ 0	
4)	Your religion did not allow to use a FP method.	Yes ☐ 1	No ☐ 0	
5)	You were afraid of health problems (side-effect).	Yes ☐ 1	No ☐ 0	
6)	You did not want to use a FP method.	Yes ☐ 1	No ☐ 0	
7)	Your partner did not want to use a FP method.	Yes ☐ 1	No ☐ 0	
8)	You used a traditional method instead.	Yes ☐ 1	No ☐ 0	
9)	You are breastfeeding.	Yes ☐ 1	No ☐ 0	
10)	Other : Specify ( )			

1 Research ID (Facility – Participant)

* Facility code	04. Chinyunyu	08. Chitemalesa
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03. Chalimbana	07. Chainda	11. Nyangwena

2 Date of Interview (DD/MM/YYYY) ☐☐ – ☐☐ – ☐☐☐☐

3 Safe Motherhood No. ☐☐☐☐ - ☐☐☐ - ☐☐☐☐☐ - ☐☐

4 Age of Baby ( )weeks

☆Confirmation of enrolment

Is this her first interview for this study?

Yes ☐ 1	→ fill in	**1) Participant list**
No ☐ 0		**2) Appointment card**
		3) Basic Information
		4) Register Data
		5) ART information sheet
		6) Enrolment sheet

A. Socio-demographic Characteristics:

Please answer about your social background.

A401. Marital status

Married	☐ 0
Living with a man	☐ 1
Divorced/Separated	☐ 2
Widowed	☐ 3
Never Married	☐ 4

A402. Estimated household income per month ***(Kwacha)***

<50,000	☐ 0
50,000-99,999	☐ 1
100,000-199,999	☐ 2
200,000-499,999	☐ 3
>500,000	☐ 4
Declined to answer	☐ 99

A403. Do you usually work? ***(Only for paid work)***

No	☐ 0
Once in a while	☐ 1
Part of the year	☐ 2
Throughout the year	☐ 3

A404. Does **<u>your partner</u>** usually work? ***(Only for paid work)***

No	☐ 0
Once in a while	☐ 1
Part of the year	☐ 2
Throughout the year	☐ 3
If no partner, N/A	☐ 98

A405. During the past month, how often have you had problems getting the food you need?

Never	☐ 0
Sometimes	☐ 1
Always	☐ 2

A406. During the past month, how often have you had a drink containing alcohol?

Never	☐ 0
Once a Month	☐ 1
2 or 3 Times a Month	☐ 2
Once or Twice a Week	☐ 3
3 or 4 Times a Week	☐ 4
5 or 6 Times a Week	☐ 5
Daily	☐ 6

A407. Do you currently smoke cigarettes?

Yes	☐ 1
No	☐ 0

A408. Did you change your residence since the last interview?

Yes	☐ 1
No	☐ 0
This is the first interview, NA.	☐ 98

B. General Health:

Please answer about your health condition.

B401. In general, would you say your health is:

Poor	☐ 0
Fair	☐ 1
Good	☐ 2
Excellent	☐ 3

B402. Have you ever had any problems (side-effects) since starting medications for HIV (ARV)?

Yes	☐ 1
No	☐ 0

B403. In general, would you say ***your baby's*** health is:

Poor	☐ 0
Fair	☐ 1
Good	☐ 2
Excellent	☐ 3

B404. Recent body weight of the baby

kg	(age by WEEK)

B405. Has ***your baby*** ever had any problems (side-effects) ***since starting medications for HIV (ARV)?***

Yes	☐ 1
No	☐ 0
If baby has never taken medication for HIV, N/A	☐ 98

C. Mental Health:

C401. Please describe how often you felt or behaved this way during the ***past week.***

- Rarely or none of the time (less than 1 day)
- Some or a little of the time (1-2 days)
- Occasionally or moderate amount of time (3-4 days)
- Most or all of the time (5-7 days)

		Less than 1 day Rare or None	1 to 2 days Some or a little	3 to 4 days Occasionally or Moderate	5 to 7 days Most or All
1)	Were you bothered by things that usually don't bother you?	☐ 0	☐ 1	☐ 2	☐ 3
2)	Did you have trouble keeping your mind on what you were doing?	☐ 0	☐ 1	☐ 2	☐ 3
3)	Did you feel depressed?	☐ 0	☐ 1	☐ 2	☐ 3

	- *Rarely or none of the time (less than 1 day)* - *Some or a little of the time (1-2 days)* - *Occasionally or moderate amount of time (3-4 days)* - *Most or all of the time (5-7 days)*	Less than 1 day Rare or None	1 to 2 days Some or a little	3 to 4 days Occasionally or Moderate	5 to 7 days Most or All
4)	Did you feel that everything you did was an effort? (Did you feel like you were too tired to do things?)	☐ 0	☐ 1	☐ 2	☐ 3
5)*	Did you feel hopeful about the future? (reverse)	☐ 3	☐ 2	☐ 1	☐ 0
6)	Did you feel fearful?	☐ 0	☐ 1	☐ 2	☐ 3
7)	Was your sleep restless?	☐ 0	☐ 1	☐ 2	☐ 3
8)*	Were you happy? (reverse)	☐ 3	☐ 2	☐ 1	☐ 0
9)	Did you feel lonely?	☐ 0	☐ 1	☐ 2	☐ 3
10)	Could you not get 'going'? (Was it hard to get started doing things?)	☐ 0	☐ 1	☐ 2	☐ 3

D. Internalized Stigma:

Please answer about how you feel or behave due to your HIV status

D402. Do you sometimes feel bad about yourself because you are HIV-positive?

Disagree	☐ 0
Unsure	☐ 1
Agree	☐ 2
Declined to answer	☐ 99

E. Partner/ Family:

Please answer about attitudes of your partner & family members to you

"Family member" includes those who lives together

E401. Do you live with your partner or adult family members?

Yes	☐ 1	
No	☐ 0	→ **Go to "F".**

E402. ***Since this pregnancy***, did your partner take a couple counselling and testing for HIV?

Yes	☐ 1
No	☐ 0
Declined to answer	☐ 99

E403. What is your partner's HIV status?

Positive	☐ 1	
Negative	☐ 0	**Go to E405.**
Unsure	☐ 2	
Declined to answer	☐ 99	

E404. Does your partner take medication for HIV (ARV)?

Yes	☐ 1
No	☐ 0
Unsure	☐ 2
Declined to answer	☐ 99

E405. Does your partner usually use a condom?

Never	☐ 0
Sometimes	☐ 1
Always	☐ 2
Declined to answer	☐ 99

E406. Have you disclosed your HIV status to your partner and adult family members?

	Partner	Family
Yes	☐ 1	☐ 1
NO	☐ 0	☐ 0
Declined to answer	☐ 99	☐ 99

E407. Do any of your family members know that you are taking medication for HIV (ARV)?

	Partner	Family	
Yes	☐ 1	☐ 1	
NO	☐ 0	☐ 0	
If the participants is not taking medication, N/A	☐ 98	☐ 98	→**Go to E410.**
Declined to answer	☐ 99	☐ 99	

E408. Does anyone in your family regularly remind you to take your medication for HIV (ARV)?

Yes	☐ 1
No	☐ 0

E409. During the past month, have you ever missed your medication for HIV (ARV) because you did not want your family members to find out?

Yes	☐ 1
No	☐ 0
Declined to answer	☐ 99

E410. Have you ever experienced the following abuse from your family since the ***current pregnancy*** ?
(Ask one by one)

1)	Verbal abuse	Yes ☐ 1	No ☐ 0	Declined to answer ☐ 99
2)	Physical violence	Yes ☐ 1	No ☐ 0	Declined to answer ☐ 99
3)	Separated or divorced from your partner	Yes ☐ 1	No ☐ 0	Declined to answer ☐ 99
4)	Forced to leave home	Yes ☐ 1	No ☐ 0	Declined to answer ☐ 99

E411. Overall, how would you rate the support you receive from your family?

Poor	☐ 0
Fair	☐ 1
Good	☐ 2
Excellent	☐ 3

F. Social Support:

Please answer about how you are supported by others

F401. Who is the most supportive person? ***on your health problem*** ***(Select only one.)***

Your partner	☐ 1
Your parent	☐ 2
Your brother/sister	☐ 3
Your son/daughter	☐ 4
Your friend	☐ 5
Other: ( )	☐ 6
Nobody	☐ 0

F402. How would you rate the care you receive from the health facility staff?

Poor	☐ 0
Fair	☐ 1
Good	☐ 2
Excellent	☐ 3

F403. Do you regularly participate in a support group of people living with HIV?

Yes	☐ 1	
No	☐ 0	→ **Go to F405.**

F404. Overall, how would you rate the support you receive from the support group?

Poor	☐ 0
Fair	☐ 1
Good	☐ 2
Excellent	☐ 3

F405. Do you regularly receive home based care?

Yes	☐ 1	
No	☐ 0	→ **Go to F408.**

F406. Does the home based caregiver regularly remind you to take your medication for HIV (ARV)?

Yes	☐ 1
No	☐ 0

F407. Overall, how would you rate the support you receive from the home based care?

Poor	☐ 0
Fair	☐ 1
Good	☐ 2
Excellent	☐ 3

F408. During the past month, have you ever felt bad because of things people did or said to you on account of your HIV status?

Yes	☐ 1
No	☐ 0
Declined to answer	☐ 99

G. Belief of the effectiveness on HIV medication:

Please answer how you believe the effectiveness of medication for HIV (ARV).

		Disagree	Agree	Don't Know
G401	Taking medication for HIV (ARV) can help keep HIV from being passed to the baby.	☐ 0	☐ 1	☐ 2
G402.	The HIV medication that you are taking makes you healthier.	☐ 0	☐ 1	☐ 2
G403.	If you do not take medications for HIV (ARV) properly, the medications won't work as well.	☐ 0	☐ 1	☐ 2

K. Feeding Practice:

Please answer how you think and practice feeding.

K401. Are you currently breastfeeding?

Yes	☐ 1	
No	☐ 0	→ **Go to K404.**

K402. What else was the baby ever given to drink or eat? ***(Ask one by one)***

1)	Milk (Other than breast milk)	Yes ☐ 1	Not ☐ 0
2)	Infant formula	Yes ☐ 1	Not ☐ 0
3)	Plain water	Yes ☐ 1	Not ☐ 0
4)	Sugar water	Yes ☐ 1	Not ☐ 0
5)	Gripe water	Yes ☐ 1	Not ☐ 0
6)	Sugar-salt water solution	Yes ☐ 1	Not ☐ 0
7)	Fruit juice	Yes ☐ 1	Not ☐ 0
8)	Tea/Infusions	Yes ☐ 1	Not ☐ 0
9)	Honey	Yes ☐ 1	Not ☐ 0
10)	Other( )	Yes ☐ 1	Not ☐ 0

K403. If your baby tested HIV negative, which feeding option will you choose?

Continue breastfeeding	☐ 0	→ **Go to *"L"***
Stop breastfeeding	☐ 1	
Unsure	☐ 2	

K404. How long did you breastfeed? ***(If never breasrfed, write zero "0".)***

(weeks/months)

K405. Why did you stop/not give breastfeeding?

I was afraid of HIV transmission to my baby through breastfeeding	☐ 1
My parents told me to stop/ not to give breastfeeding.	☐ 2
My partner told me to stop / not to give breastfeeding.	☐ 3
Other: Specify( )	☐ 4

L. HIV test for baby:

Please answer about HIV test for your baby.

L401. Has your baby ever been tested for HIV?

Yes, tested. (dd/mm/yyyy)		→ **Go to "*M*"**
Never tested	☐ 0	

L403. Why your baby was not tested for HIV? ***(Ask one by one.)***

1)	Health workers did not inform you about HIV test for your baby.	Yes ☐ 1	No ☐ 0
2)	You did not know why your baby should be tested.	Yes ☐ 1	No ☐ 0
3)	You did not know when your baby should be tested.	Yes ☐ 1	No ☐ 0
4)	You did not know the place where your baby should be tested.	Yes ☐ 1	No ☐ 0
5)	You were afraid of knowing the HIV status of your baby.	Yes ☐ 1	No ☐ 0
6)	You thought your baby looked healthy.	Yes ☐ 1	No ☐ 0
7)	You were afraid of stigma against your baby.	Yes ☐ 1	No ☐ 0
8)	Taking your baby to HIV test on another day was tiring.	Yes ☐ 1	No ☐ 0
9)	You were too busy to take your baby to HIV test.	Yes ☐ 1	No ☐ 0
10)	You had no transportation to take your baby to HIV test.	Yes ☐ 1	No ☐ 0
11)	You had no money to take your baby to HIV test.	Yes ☐ 1	No ☐ 0
12)	Other: Specify ( )		

M. Family Planning:

Please answer about various ways or methods that a couple can use to delay or avoid a pregnancy.

M401. Do you want to have more children?

Yes	☐ 1
No	☐ 0

M402. Did any health workers tell you about any methods to delay or avoid pregnancy after the delivery?

Yes	☐ 1
No	☐ 0

M403. Are you currently using any method to delay or avoid getting pregnant?

Yes	☐ 1	
No	☐ 0	→ **Go to M405.**

M404. ***If Yes at M403,*** what method are you using? ***(Ask one by one)***

1)	Male condom	Yes ☐ 1	No ☐ 0	**After answer, Go to "H".**
2)	Pill	Yes ☐ 1	No ☐ 0	
3)	Injection	Yes ☐ 1	No ☐ 0	
4)	Other ( )			

M405. ***If No at M403***, why don't you use any methods to delay or avoid a pregnancy (=FP methods)? ***(Ask one by one)***

1)	You do not know any FP methods.	Yes ☐ 1	No ☐ 0
2)	You do not know where you can get a FP method.	Yes ☐ 1	No ☐ 0
3)	You do not ask health worker for a FP method.	Yes ☐ 1	No ☐ 0
4)	Your religion does not allow to use a FP method.	Yes ☐ 1	No ☐ 0
5)	You are afraid of health problems (side-effect).	Yes ☐ 1	No ☐ 0
6)	You do not want to use a FP method .	Yes ☐ 1	No ☐ 0
7)	Your partner does not want to use a FP method.	Yes ☐ 1	No ☐ 0
8)	You used a traditional method instead.	Yes ☐ 1	No ☐ 0
9)	You are breastfeeding.	Yes ☐ 1	No ☐ 0
10)	You want to have more children.	Yes ☐ 1	No ☐ 0
11)	Other : Specify ( )		

M406. Do you want to use any method to delay or avoid a pregnancy in the future?

Yes	☐ 1
No	☐ 0

H. ART clinic visit: New HIV+ mothers & Already known HIV status but not yet on ART mothers

Please answer about starting HIV treatment

H401 When did you know your HIV positive status?

Before this pregnancy	☐ 1	
During this pregnancy	☐ 0	→ **Go to H403.**

H402 Please answer about "before the current pregnancy" one by one.

1)	***Before the current pregnancy*** , did you regularly attend ART clinic?	Yes ☐ 1	No ☐ 0	**All=No, Go to H403.**
2)	***Before the current pregnancy*** , have you already had your ART card?	Yes ☐ 1	No ☐ 0	**1) or 2) =Yes but 3)=NO, go to H403.**
3)	***Before the current pregnancy*** , have you already been on ART?	Yes ☐ 1	No ☐ 0	**3)=Yes, go to "N".**

H403. Did health workers tell you to go to ART clinic for blood test / treatment?

Yes	☐ 1
No	☐ 0

H404. Did you have blood test (for CD4)?

Yes	☐ 1	
No	☐ 0	→ **Go to H410.**
Don't know	☐ 2	

H405. When was the test? (mm) (yyyy)

H406. Which facility? (Name of health facility)

H407. Did you receive the results of blood test?

Yes	☐ 1
No	☐ 0
Don't know	☐ 2

H408. ***After you received the result… (Ask one by one.)***

1) You were given another appointment for another test after (days/week/months) — Yes ☐ 1 No ☐ 0
after (days/weeks/months)

2) You were given an appointment to start lifelong treatment after(days/weeks/month) — Yes ☐ 1 No ☐ 0
after (days/weeks/months)

3) You started lifelong treatment — Yes ☐ 1 No ☐ 0
Started on (dd/mm/yyyy) → **Go to *"N"***

H409. ***If answer is NO at H407,*** what were the reasons for not receiving the result of blood test?

The result was not ready	☐ 1	**Go to *"N"***
I didn't go back to receive results	☐ 2	
Others (specify)	☐ 3	

H410. Why didn't you go for blood test (ART clinic)? ***(Ask one by one.)***

1)	Health workers did not inform you to visit ART clinic.	Yes ☐ 1	No ☐ 0
2)	You did not know why you should go to ART clinic.	Yes ☐ 1	No ☐ 0
3)	You did not know when you should go to ART clinic.	Yes ☐ 1	No ☐ 0
4)	You did not know the place where you should go to ART clinic.	Yes ☐ 1	No ☐ 0
5)	You did not believe your HIV status.	Yes ☐ 1	No ☐ 0
6)	You thought treatment for HIV is harmful.	Yes ☐ 1	No ☐ 0
7)	You felt healthy without treatment.	Yes ☐ 1	No ☐ 0
8)	You thought HIV can not be cured by treatment.	Yes ☐ 1	No ☐ 0
9)	You were afraid of stigma.	Yes ☐ 1	No ☐ 0
10)	You were scared of the marriage ending.	Yes ☐ 1	No ☐ 0
11)	Visiting ART clinic on another day was tiring.	Yes ☐ 1	No ☐ 0
12)	Visiting another facility for ART clinic was tiring.	Yes ☐ 1	No ☐ 0
13)	You were too busy to visit ART clinic.	Yes ☐ 1	No ☐ 0
14)	You had no transportation to visit ART clinic.	Yes ☐ 1	No ☐ 0
15)	You had no money to visit ART clinic.	Yes ☐ 1	No ☐ 0
16)	Other: (Specify		)

N. Adherence to HIV medication (ARV) : 6 weeks to 5 months after delivery

N401. During this pregnancy and after this delivery, do (did) you take the medication for HIV?

Yes	☐ 1	
No	☐ 0	→ **Go to "P"**

N402. How many ***times*** do (did) you take medication ***per day***? ☐☐ times

N412. ***During pregnancy***, how much did you ***MISS*** HIV medications ?
Using a line below, please point at approximate amount of medication you took.
Interviewer puts a tick where the participant points.

N413. ***During labour and delivery***, did you take medication for HIV (ARV)?

Yes	☐ 0
No	☐ 1
Unsure	☐ 2

N414. ***Regarding the 7-days HIV medication (ARV) just after delivery,***
how many days did you ***Miss***?
Note: If you miss at least once in a day, it is counted as 1day.

N415. Most medications need to be taken on a ***schedule***. For example "2 times a day" or "every 12 hours".
How many days did you ***Miss*** your ***specific schedule*** for the ***7-days HIV medication just after delivery***?

The questions below are only for women on lifelong treatment (ART).
If the participant is not on the treatment (ART), Go to N410.

Please answer about medications for HIV (ARV) that you may have missed taking ***over the last 4 days.***
We understand that many people on medications for HIV (ARV) find it difficult to take it regularly,
and often missed doses. We won't be surprised if you have missed lots of doses as well.

N404. ***Missed Medication:***

How many times did you ***miss*** during ***the last 4 days?***

Note that the table asks about TIMES, not the numbers of PILLS.

Never missed = 0 **Once missed =1** **Twice missed = 2**	Write a number in each blank →	Yesterday	2 days ago	3 days ago	4 days ago
		times missed	times missed	times missed	times missed

N405. ***Missed Time Schedule:***

Most medications need to be taken ***on a schedule***,

For example, "twice a day" or "every 12 hours".

How often did you ***miss*** your ***specific schedule over the last 4 days?***

(Select only ONE)

Never 0 day	Some 1 day	About Half 2 days	Most 3days	All 4 days
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

N408. ***Last Time Missed:***

When was ***the last time*** you ***missed*** any of your medications?

(Select only ONE)

Within the past week	☐ 0
1-2 weeks ago	☐ 1
2-4 weeks ago	☐ 2
1-3 months ago	☐ 3
More than 3 months ago	☐ 4
Never skip medications	☐ 5

Go to N411.

N409. Adherence in ***the past 30 days***

Tick in the blank below at the point showing you best guess about **HOW MANY DAYS** you have **MISSED** any medications in **the last 30 days**.

For example, if you missed 2 days, you tick in a blank of "1-3 days"

Note: If you miss at least once in a day, it is counted as 1day.

Never Missed ☺ ALL Missed ☹

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Never	1-3days	4-6days	7-9days	10-12days	13-15days	16-18days	19-21days	22-24days	25-27days	28-30days

N410. If you missed your medications in ***the last 30 days***, what were the reasons?

If your medication for HIV has finished 7 days after delivery, please answer about ***the last 30 days before ending HIV medication.***

(Ask one by one.)

1)	You simply forgot.	Yes ☐ 1	No ☐ 0
2)	You were away from home.	Yes ☐ 1	No ☐ 0
3)	You were busy with other things.	Yes ☐ 1	No ☐ 0
4)	You had a change in daily routine.	Yes ☐ 1	No ☐ 0
5)	You fell asleep/slept through dose.	Yes ☐ 1	No ☐ 0
6)	You had problems taking medications at specific time.	Yes ☐ 1	No ☐ 0
7)	You felt sick.	Yes ☐ 1	No ☐ 0
8)	You wanted to avoid side effects.	Yes ☐ 1	No ☐ 0
9)	You felt depressed/ overwhelmed.	Yes ☐ 1	No ☐ 0
10)	You had too many pills to take.	Yes ☐ 1	No ☐ 0
11)	You did not want others to notice you taking drugs.	Yes ☐ 1	No ☐ 0
12)	You felt drug was toxic/harmful.	Yes ☐ 1	No ☐ 0
13)	Your partner interfered with your medication.	Yes ☐ 1	No ☐ 0
14)	You did not have enough food.	Yes ☐ 1	No ☐ 0
15)	Other(		)

N411. Refill record ***since the first antenatal*** visit of the current pregnancy (dd/mm/yyyyy)

	Visited date
1	
2	
3	
4	
5	
6	
7	
8	
9	

P. Baby Adherence: 6 weeks to 5 months after delivery

Please answer about medication for your baby.

P401. Currently does **your baby** take Septrin?

Yes	☐ 1
No	☐ 0
Unsure	☐ 2

P402. ***Mother's knowledge on baby's medication***
Currently does **your baby** take medications for HIV ?
(medication other than Septrin)?

Yes	☐ 1	→**Go to P404.**
No	☐ 2	
Unsure	☐ 3	

P403. ***Confirmation of giving HIV medication to baby***
Please show me the medicine for your baby.
(Please check the register book as well.)

The baby has Nevirapine	☐ 1	
The baby doesn't have Nevirapine	☐ 0	→**End the interview.**

P404. Who mainly gives HIV medication to **your baby**?

Yourself	☐ 1	
Your partner	☐ 2	**Go to P408.**
Other ( )	☐ 3	

P405. Does anyone in your family regularly remind you
to give medication for HIV (ARV) to your baby?

Yes	☐ 0
No	☐ 1

P406. Is it difficult for you to understand
the instruction of how to give
HIV medication to your baby?

Easy	a little Easy	a little Difficult	Difficult
☐ 0	☐ 1	☐ 2	☐ 3

P407. Is it difficult for you to use a syringe
when giving HIV medication
to your baby?

Easy	a little Easy	a little Difficult	Difficult
☐ 0	☐ 1	☐ 2	☐ 3

P408. For the HIV medicaton (NVP) of your baby,
How much do you give the HIV medication per 1 time?

ml per 1 time

P417. Regarding ***6-weeks HIV medication*** since **your baby** started medications,
how much HIV medications did your baby ***MISS*** ?
Using a line below, please point at approximate amount of medication your baby took.
(Interviewer puts a tick where the participant points.

The next questionnaire asks about medication for HIV (ARV)
that **your baby** has **MISSED** to take over **the last 4 days.**
We understand that many mothers find it difficult to give it to their babies regularly.
We won't be surprised if your baby have missed lots of doses as well.

P409. ***Missed Medication:***
How many ***TIMES*** did ***your baby MISS*** to take the medications
in the ***last 4 days*** ? **(Fill in each blank)**

		Yesterday	2 days ago	3 days ago	4 days ago
Never missed = 0					
Once missed =1	Write a number	times	times	times	times
Twice missed = 2	in each blank →	missed	missed	missed	missed

P410. ***Missed Time Schedule:***

Most medications need to be taken ***on a schedule.*** For example taking at specific time.

How often did you ***MISS*** the specific schedule for your baby over the ***last 4 days*** ?

Never	Some	About Half	Most	All
0 day	1 day	2 days	3days	4 days
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

P413. ***Last Time Missed:***

When was ***the last time*** ***your baby*** ***MISSED*** any of HIV medications?

(Select only ONE.)

Within the past week	☐ 0	
1-2 weeks ago	☐ 1	
2-4 weeks ago	☐ 2	
More than 4 weeks ago	☐ 3	
Never skip medication	☐ 4	→**Go to P416.**

P414. ***Adherence since baby starting medication for HIV (ARV):***

Tick in the blank below at the point showing you best guess about

HOW MANY DAYS *your baby have* ***MISSED*** *any medications in* ***the last 30 days*** *.*

For example, if your baby missed 2 days, you tick in a blank of "1-3 days"

Note: If your baby miss at least once in a day, it is counted as 1day.

Never Missed ☺ ALL Missed ☹

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Never	1-3days	4-6days	7-9days	10-12days	13-15days	16-18days	19-21days	22-24days	25-27days	28-30days

P415. If you ***missed*** giving HIV drugs to **your baby** in the ***last 30 days*** ,

what are the reasons? **(Ask one by one)**

1)	You simply forgot.	Yes ☐ 1	No ☐ 0
2)	You were away from home.	Yes ☐ 1	No ☐ 0
3)	You were busy with other things.	Yes ☐ 1	No ☐ 0
4)	You had a change in daily routine.	Yes ☐ 1	No ☐ 0
5)	Your baby fell asleep/slept through dose.	Yes ☐ 1	No ☐ 0
6)	You had problems giving medications at specific time.	Yes ☐ 1	No ☐ 0
7)	Your baby was sick.	Yes ☐ 1	No ☐ 0
8)	You wanted to avoid side effects.	Yes ☐ 1	No ☐ 0
9)	You felt depressed/ overwhelmed.	Yes ☐ 1	No ☐ 0
10)	Your baby had too many medications to take.	Yes ☐ 1	No ☐ 0
11)	You didn't want others to notice your baby taking medicine.	Yes ☐ 1	No ☐ 0
12)	You felt drug was toxic/harmful for your baby.	Yes ☐ 1	No ☐ 0
13)	Your partner interfered with giving the medication to your baby.	Yes ☐ 1	No ☐ 0
14)	Your baby did not take enough milk/fluid.	Yes ☐ 1	No ☐ 0
15)	Other( )		

P416. Refill record since baby was born ***(dd/mm/yyyy)***

	Visited date
1	
2	
3	
4	
5	
6	

End of the interview : Thank the woman, give a soap, and make a next appointment.

Appendix 7. Informed Consent Form

Explanation Sheet

MoH Zambia – JICA SHIMA project-The University of Tokyo

Prevention of mother-to-child transmission of HIV and its linkages to ART Services in Chongwe

The purpose of this study is to assess current situation of HIV care, support and treatment for pregnant women/mothers and babies in the district in order to improve services provided in the district. We would like you to participate in the study. What we learn from you will contribute to improve prevention of mother-to-child HIV transmission services in Zambia and other countries in the future.

If you agree with this study, we would like you to participate in the interviews **during pregnancy, 7 days, 6 weeks, and 6 month after delivery.** In each interview, we will ask you about your background, health condition, your baby's health condition, clinical information, care, treatment, and medication. We would like to see your antenatal card, children's clinic card, and medical record.

We would like to inform you that your response will be kept confidential. The information will not be communicated to anyone except the research team. You will be interviewed privately at your comfort. Although your participation is much appreciated, your participation is voluntary and you are free to withdraw from the study at any time and all the data will be deleted at the time of your withdrawal. Your participation and response will not affect the quality of care you receive at the care facility. Please read next page and if you agree then sign the document. If you feel comfortable and allow us, I would like to start the interview. It will take about 40-50 minutes. If you have any questions or concerns about the study please don't hesitate to contact the following address as given below.

We will highly appreciate your support. Thank you for your cooperation.

- Charles Msiska (Director, Chongwe District Health Office)
  Chongwe District Health Office Tel: 211-620-023

- Naoko Ishikawa (Chief Advisor, SHIMA project / MoH Zambia - JICA)
  Ministry of Health, Ndeke House, P.O.Box 30205, Lusaka Tel&fax: 211-257-728
- The University of Zambia Research Ethics Committee
  Ridgeway Campus P.O. Box 50110 Telex: UNZALU ZA 44370

  Telegrams: UNZA, LUSAKA Tel: 260-1-256067 Fax: + 260-1-250753

- Masamine Jimba, Sumiyo Okawa (The University of Tokyo)
  7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan Tel: +81-3-5841-3698

Informed Consent Form

I acknowledge that:

- I have been given all the information regarding the research.
- I have been told that confidentiality and privacy will be maintained, and any information I will give will not be disclosed by any means.
- I and my child are not under any pressure to contribute to the research.
- I clearly know that I and my child can quit answering questions at any stage and no action will be taken against me and my child.
- I am satisfied with the information given.

□ I agree to participate in the study.

□ I agree my child to participate in the study.

Name: _____ Signature:

Name (Researcher):

Date(dd/mm/yy):

Please note:

If you need any information, please do not hesitate to contact the following address as given below:

- Charles Msiska (Director, Chongwe District Health Office)
  Chongwe District Medical Office Tel: 211-620-023

- Naoko Ishikawa (Chief Advisor, SHIMA project / MoH Zambia - JICA)
  Ministry of Health, Ndeke House, P.O.Box 30205, Lusaka Tel&fax: 211-257-728
- The University of Zambia Research Ethics Committee
  Ridgeway Campus P.O. Box 50110 Telex: UNZALU ZA 44370
  Telegrams: UNZA, LUSAKA Telephone: 260-1-256067 Fax: + 260-1-250753

- Masamine Jimba, Sumiyo Okawa (The University of Tokyo)
  7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan Tel: +81-3-5841-3698

Appendix 8: Ethical Approval by the Research Ethics Committee

of the University of Tokyo

様式第２号

倫　理　委　員　会
審 査 結 果 報 告 書

平成２３年４月２６日

申請者
国際地域保健学
教授
神馬　征峰　殿

東京大学大学院医学系研究科長・医学部長
宮園　浩平　印

審査番号　3261-(1)
研究課題　ザンビア国における HIV 母子感染予防の服薬アドヒアランスに関する前向きコホート調査

上記研究計画を審査番号 3261 の軽微な変更と認めます。
ここに通知します。

判　定 ○承認する。　　承認しない。 条件付きで承認する。　　該当しない。 変更を勧告する。
条件あるいは変更勧告の理由（細則第３条第２項）

様式第２号

倫　理　委　員　会
審　査　結　果　報　告　書

平成２２年１１月２９日

申請者
国際地域保健学
教授
神馬　征峰　殿

東京大学大学院医学系研究科長・医学部長
清水　孝雄　印

審査番号　3261
研究課題　ザンビア国 HIV 母子感染予防内服の家庭訪問によるアドヒアランス支援：マザー・ベビーパックの有効性を高める介入研究

上記研究計画を平成２２年１１月２９日の委員会で審査し下記のとおり判定しました。
ここに通知します。

判　定 ○承認する。　　承認しない。 条件付きで承認する。　　該当しない。 変更を勧告する。
条件あるいは変更勧告の理由（細則第３条第２項）

Appendix 9: Ethical Approval by the Biomedical Research Ethics Committee of the University of Zambia

THE UNIVERSITY OF ZAMBIA

BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
Telegrams: UNZA, LUSAKA
Telex: UNZALU ZA 44370
Fax: + 260-1-250753
E-mail: unzarec@unza.zm or unzarec@coppernet.zm

Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia

Assurance No. FWA00000338
IRB00001131 of IORG0000774

11 December, 2009
Ref.: 022-11-09

Dr Ikuma Nozaki, MD
JICA, HIV/AIDS Care Project Expert
C/O JICA Zambia Office
P.O. Box 30027
10101 Lusaka, Zambia

Dear Dr Nozaki,

RE: SUBMITTED RESEARCH PROPOSAL: **"EFFICACY AND IMPACTS OF ANTIRETROVIRAL THERAPY (ART) IN RURAL AREAS, ZAMBIA"**

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 23 October, 2009 where changes were recommended. We acknowledge receipt of the revised proposal with corrections/clarifications. The proposal is approved.

CONDITIONS:

- This approval is based strictly on your submitted proposal. Should there be need for you to modify or change the study design or methodology, you will need to seek clearance from the Research Ethics Committee.
- If you have need for further clarification please consult this office. Please note that it is mandatory that you submit a detailed progress report of your study to this Committee every six months and a final copy of your report at the end of the study.
- Any serious adverse events must be reported at once to this Committee.
- Please note that when your approval expires you may need to request for renewal. The request should be accompanied by a Progress Report (Progress Report Forms can be obtained from the Secretariat).
- **Ensure that a copy of final results of the study is submitted to this Committee.**

Yours sincerely,

Dr James Munthali
A/CHAIRPERSON

Date of approval: 11 December, 2009 **Date of expiry:** 10 December, 2010

THE UNIVERSITY OF ZAMBIA

BIOMEDICAL RESEARCH ETHICS COMMITTEE

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Lusaka, Zambia

PROGRESS REPORT FORM

The University of Zambia Research Ethics Committee (UNZAREC) would like to know how your study has progressed so far, and if any difficulties have been experienced. Please complete the questionnaire below and return, within two weeks, to:-

The Secretary
UNZA Research Ethics Committee
School of Medicine
P.O. Box 50110
LUSAKA

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1. **Name(s) of Principal Investigator(s):**

1) Zambian side;
Dube, Christopher, District Director of Health, Mumbwa, GRZ
Msiska, Charles, District Director of Health, Chongwe, GRZ
Sialubanga, District Director of Health, Kalomo, GRZ
Hadunka, F, District Director of Health, Kazungula, GRZ
Mwango, Albert, National ARV coordinator, MOH, GRZ
Izukanji Sikazwe, ART Programme Officer, MOH, GRZ
Siakantu, Gardner, Acting Director of Directorate of Clinical Care and Diagnostic Services, MOH, GRZ

2) Japanese side;
Nozaki, Ikuma, JICA HIV/AIDS Care Expert/ International Medical Centre of Japan, Tokyo, Japan
Komada, Kenichi, JICA HIV/AIDS Care Expert/ International Medical Centre of Japan, Tokyo, Japan
Miyano, Shinsuke, JICA HIV/AIDS Care Expert/ International Medical Centre of Japan, Tokyo, Japan
Ishikawa, Naoko, JICA Chief Adviser/ International Medical Centre of Japan, Tokyo, Japan
Kakimoto Kazuhiro, International Medical Centre of Japan, Tokyo, Japan

Collaborators:
Manyepa, Pauline, HIV/AIDS coordinator, Livingstone DHMT, GRZ (Sister in charge, Livingstone Sepo Centre)
Kuriyama, Mika, Livingstone Sepo Centre/JICA JOCV
Miyamoto, Hideki, International Medical Centre of Japan, Tokyo, Japan
Sonoda, Miwa, International Medical Centre of Japan, Tokyo, Japan
Anami, Midori, International Medical Centre of Japan, Tokyo, Japan
Sasaki, Yuri, the University of Tokyo, Tokyo, Japan
Okawa, Sumiyo, the University of Tokyo, Tokyo, Japan