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ORIGINAL ARTICLE

HIV-Positive Women Taking Lifelong Antiretroviral Therapy Report Better Adherence Than Women Taking Short-Course Prophylaxis During and After Pregnancy Under PMTCT Program Option A in Lusaka, Zambia

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ABSTRACT

Background and Objectives: HIV-positive women's adherence to antiretrovirals is critical for prevention of mother-to-child transmission. We aimed to establish if mothers taking triple lifelong antiretroviral therapy report higher adherence compared to mothers taking short-course prophylaxis under Option A in Lusaka, Zambia.

Methods: In this clinic-based cross-sectional study, we interviewed 320 HIV-positive mothers at a large public health facility in Lusaka in 2014. Participants reported adherence using a visual analog scale. Multiple logistic regression models were used to determine the adjusted odds of adherence by mother's prescribed regimen.

Results: Women taking lifelong triple antiretroviral therapy report higher adjusted odds of adherence during pregnancy, postpartum, and to giving the infant prophylaxis compared to women to women taking short-course prophylaxis.

Discussion: Women on lifelong therapy may have better adherence compared to women on short course prophylaxis because they knew their positive status for longer or were symptomatic with HIV-related disease. The lifelong therapy regimen may be easier for women to follow, particularly because they are required to give the infant prophylaxis for a shorter duration of time.

Conclusions and Global Health Implications: Our results indicate that lifelong triple antiretroviral therapy has the potential to promote better drug adherence during and after pregnancy among women living with HIV in sub-Saharan Africa, compared to short-course antiretroviral regimens.

Key words: HIV-positive Women • Prevention of Mother-to-Child Transmission • Antiretroviral Therapy • Adherence • Zambia • Option A • PMTCT • ART

1. Background and Objectives

As part of the effort to eliminate mother-to-child transmission of HIV, the World Health Organization (WHO) in 2010 introduced two prevention of mother-to-child transmission (PMTCT) programmatic options, "Option A" and "Option B," which countries adopted based on their individual health care system capabilities. Under Option A, two distinctly different antiretroviral (ARV) regimens (described below) were prescribed for pregnant or breastfeeding women based on their clinical and immunological status; while under Option B, triple antiretroviral therapy (ART) is prescribed to all HIV-positive pregnant or breastfeeding women, but only those meeting specific clinical requirements continue ART for life. Zambia opted for Option A, under which only HIV-positive pregnant or breastfeeding women with a low CD4 cell count (≤350 cells/mm) or WHO clinical stage 3 or 4 initiated lifelong triple ART.[1] Women who were not eligible for treatment (i.e., CD4 count >350) under Option A initiated a short-course ARV prophylaxis regimen taken during pregnancy and throughout the breastfeeding period. In 2011, Malawi pioneered a new PMTCT regimen, Option B+, which initiates all HIV-positive pregnant or breastfeeding women onto lifelong triple ART regardless of their CD4 count or clinical stage.[2]

One neglected factor in countries' PMTCT programmatic decisions is which ARV regimens promote the best adherence during and after pregnancy. Some researchers hypothesize that the simplification of the drug regimen with Option B+ may help to improve women's adherence during and after pregnancy.[3, 4] However, to our knowledge, no studies to-date have established that the triple ART regimen results in better adherence among HIV-positive pregnant or breastfeeding women compared to the short-course ARV prophylaxis regimen used under Option A. This knowledge is crucial because high adherence to ARVs among HIV-infected pregnant and breastfeeding women is linked to numerous beneficial health outcomes, including preventing vertical (i.e., mother-to-child) HIV transmission, maternal HIV-related disease progression, and drug resistance for both the mother and the infant.[5-9] Recent studies indicate adherence levels of at least 70-80% of medication doses are required in HIV-positive patients to adequately suppress the virus using the current combination antiretroviral therapy (cART) drugs.[7-9]

Adherence to ARVs for PMTCT varies vastly across studies from sub-Saharan Africa. Some PMTCT studies report maternal adherence levels as high as 98% of women in urban Kenya,[10] to as low as 38% of women in rural Uganda.[11] Notably, there is no universal measurement for PMTCT adherence; data come from vastly different ARV regimens, adherence measures (e.g., self-reports, pill count, or biomarkers), thresholds of adherence, and time periods (i.e., antepartum, intrapartum, or postpartum).[12] This makes comparison of ARV adherence across different regimens under the WHO programmatic options difficult.

The objective of this study was to determine if HIV-positive women report better adherence to lifelong triple ART compared to short-course ARV prophylaxis under Option A in a large urban health center in Lusaka, Zambia. We also examined why adherence may differ for women on lifelong ART compared to those on short-course prophylaxis, and how this would inform countries transitioning or considering transitioning to Option B+. Moving forward, countries in sub-Saharan Africa should aim to implement national PMTCT programs that are not only biomedically effective but also maximize HIV-positive women's adherence during and after pregnancy. The study findings are also timely given the current move towards Option B+ across many countries in sub-Saharan Africa where all HIV-positive pregnant or breastfeeding women are expected to initiate lifelong triple ART.

2. Methods

2.1. Design

This was a secondary analysis of data from a cross-sectional study focused on adherence across the PMTCT cascade of care and gender power dynamics within heterosexual couples. A cross-sectional survey was verbally administered in the local languages by trained Zambian research assistants to HIV-positive postpartum married women who had brought their

children for pediatric immunizations at a large urban health center in Lusaka, Zambia from March to August of 2014. The research protocol was approved by the Colorado Multiple Institutional Review Board (COMIRB) and the Excellence in Research Ethics and Science (ERES) Converge IRB in Lusaka, Zambia. Written informed consent or a thumbprint was obtained from all participants.

2.2. Participants

Participants were 320 HIV-positive postpartum women who were either married or living with a man as if married and had brought a biological infant between three to nine months of age for immunizations. Infant age criterion was selected based on the Zambian immunizations schedule to capture the majority of essential PMTCT protocols and limit recall bias. Women were recruited during pediatric immunizations to participate in the survey after completing their health care visit. Eligibility was determined using the infant's "Under-Five Card," a mother's copy of her child's health record that she is required to bring to all health care visits and includes the child's birth date, height and weight, immunizations, medications, and PMTCT record. Nurses providing childhood immunizations examined women's Under Five Cards and verbally invited eligible women to proceed to a designated confidential space in the clinic. There, the research assistant explained the study, obtained informed consent, asked additional screening questions, and verbally administered the survey questionnaire. The survey was administered on paper forms in the local languages, Nyanja or Bemba. The response rate for recruited women was 85%.

2.3. Measurement

The study's main outcome of interest was medication adherence during and after pregnancy. Questions regarding medication adherence during and after pregnancy were developed from Simoni et al.'s (2006) recommendations for best practices of ART adherence self-reported measures[13] and the 2010 Malawi Demographic and Health Survey (DHS) PMTCT questions.[14] At the time of the study, Zambia was following WHO Option A (Table 1). Under this programmatic option, pregnant or breastfeeding women who were eligible for lifelong treatment (i.e., had a CD4 count below 350) received a lifelong fixed-dose combination of either: zidovudine+ lamivudine+Nevirapine (AZT+3TC+NVP);Tenofovir+ Lamivudine/Emtricitabine+Nevirapine (TDF+[3TC

Table 1: WHO options for PMTCT programs at the time of the study in 2014

Option	Woman receives		Infant receives
	Treatment (for CD4 count<350 cells/mm)	Prophylaxis (for CD4 count>350 cells/mm)	
A*	Triple ARVs starting as soon as diagnosed, continued for life	Antepartum: AZT_1 starting as early as 14 weeks gestation Intrapartum: At onset of labor, single dose NVP and first dose of AZT/3TC[2] Postpartum: Daily AZT/3TC through 7 days postpartum	Daily NVP from birth until 1 week after cessation of all breastfeeding; or, if not breastfeeding or if mother is on treatment, through age 4-6 weeks
Same initial ARVs for both:			
B	Triple ARVs starting as soon as diagnosed, continued for life	Triple ARVs starting as early as 14 weeks gestation and continued intrapartum and through childbirth if not breastfeeding or one week after cessation of all breastfeeding	Daily NVP or AZT from birth through 4-6 weeks regardless of infant feeding method
Same treatment and prophylaxis:			
B+	Regardless of CD4 count, triple ARVs starting as soon as diagnosed, continued for life		Daily NVP or AZT from birth through 4-6 weeks regardless of infant feeding method

[1]AZT=zidovudine, [2]AZT/3TC=zidovudine/lamivudine, Source: WHO, 2012 Programmatic Update: Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants

or FTC]+NVP); zidovudine+ Lamivudine+Efavirenz (AZT+3TC+EFV); or, Tenofovir+Lamivudine/Emtricitabine+Efavirenz (TDF+[3TC or FTC]+EFV).[1] HIV-exposed infants born to women taking lifelong triple ART received six weeks of infant Nevirapine (NVP) prophylaxis.

Conversely, pregnant or breastfeeding women who were not eligible for lifelong triple ART under Option A were put on the "short-course ARV prophylaxis" regimen, which included AZT prophylaxis twice daily beginning from 14 weeks gestation continued through pregnancy; intrapartum single dose NVP (sdNVP) and the first dose of AZT/3TC; and postpartum daily AZT/3TC for 7 days. HIV-exposed infants born to women taking short course prophylaxis were expected to receive NVP prophylaxis throughout the entire breastfeeding period.[1] Women on the short course regimen who chose not to breastfeed were to provide their infants with NVP prophylaxis for 6 weeks postpartum.

In our survey, both women on lifelong ART and short-course ARV prophylaxis reported on their adherence during and after pregnancy and to giving the infant NVP prophylaxis. First, participants reported if they were taking lifelong ART, and if not, if they were offered short-course ARVs during and after pregnancy. Second, participants reported their estimated adherence levels from 0 to 100% during pregnancy, postpartum, and to giving the infant NVP prophylaxis (if they were offered medication during the respective time periods) using a visual analog scale (VAS),[13] which was verbally explained to participants by the research assistants. During the postpartum time period, women taking lifelong ART reported on their drug adherence since giving birth to the time of the survey, while women on short-course prophylaxis reported on their adherence during the 7 days after childbirth. Women on lifelong ART also reported on their adherence to giving the infant NVP prophylaxis for the six week period after childbirth, while women on short-course ARV prophylaxis reported on their adherence to giving infant NVP prophylaxis since birth to the time of the survey. Drug adherence was examined as a binary outcome and defined as the woman taking (or giving to the infant) at least 80% of doses during each time period in the continuum of care based on recent literature standards.[12,15]

Self-reported adherence is one of the most common methodologies used to collect data on drug adherence and has been shown to be positively associated with plasma drug levels.[16,17] Biomarker data was not available for this study; however, research assistants used PMTCT appointment records to validate women's self-reported adherence during the interviews. For example, if a woman reported 100% adherence, but had missed multiple appointments, the interviewer would probe the participant to clarify where she was getting the medication or if she was telling the truth about her adherence.

The study's main independent variable was PMTCT regimen; it was measured based on women's self-reports of taking either lifelong triple ART or short course ARV prophylaxis during and after the most recent pregnancy. Covariates included the participant's age, the infant's age, parity, gestational age at first antenatal care (ANC) visit, whether the woman was diagnosed with HIV during this most recent pregnancy (or knew her status prior to becoming pregnant), highest educational attainment, knowledge of PMTCT, and a standardized wealth index score,[18] which was based on the number of reported household assets. With the exception of when the woman was diagnosed with HIV, all covariate questions were taken directly from the Zambian Demographic and Health Survey (DHS) questionnaire.[19]

Knowledge of PMTCT was measured by four questions on the survey[19] that were analyzed as a single count variable based on the number of correct answers, for example, "Can HIV be transmitted from a mother to her baby during pregnancy?" and "Are there any special drugs that a doctor or nurse can give to a woman infected with HIV to reduce the risk of transmission to the baby?" We measured socioeconomic status on the survey by asking participants what household assets they owned from a list of 21 possible items (e.g., electricity, a television, a refrigerator), which was subsequently converted into a linear index using principal-component

analysis (PCA) to derive weights.[18] The index was standardized prior to inclusion in the multiple logistic regression models.

2.4. Data entry and analysis

Survey data were double entered into CSPro[20] and exported into Stata 12[21] for analysis. Surveys with more than 50% missing data (n=4) were not included in the analyses. Missing data (2.3%) were imputed using multivariate chained equations in Stata 12.[22] Data converged, indicating that the multivariate chained model was a good fit for the dataset.[23] Using the imputed dataset, descriptive statistics highlighted the proportion of women who took at least 80% of medication doses during and after pregnancy, and to giving the infant NVP prophylaxis. Simple logistic regression models analyzed significant differences in adherence by regimen type for each protocol. Subsequently, multiple logistic regression models determined the adjusted odds of women reporting at least 80% drug adherence during and after pregnancy, and to giving the infant NVP prophylaxis by type of regimen and controlling for covariates.

3. Results

Sample characteristics for the 320 participants in this study have been reported elsewhere.[24] Figure 1, however, displays the descriptive results for participants' self-reported drug adherence among the two regimen types. During pregnancy, a greater proportion of women on lifelong triple ART reported taking at least 80% of their drug doses compared to women taking short-course prophylaxis: 94% and 81%, respectively ($p<0.01$). Similarly, a greater proportion of women on lifelong triple ART reported at least 80% drug adherence postpartum compared to women taking short course prophylaxis: 95% and 83%, respectively ($p<0.01$). The largest difference, however, was seen in achieving at least 80% adherence to giving the infant NVP prophylaxis. While only 76% of women on the short-course ARV prophylaxis regimen reported achieving 80% adherence to giving their infant NVP prophylaxis since birth, 93% of women on the lifelong triple ART regimen reported achieving at least 80% adherence to giving the infant NVP prophylaxis for six weeks postpartum ($p<0.001$).

In the multiple logistic regression models, women on lifelong triple ART had higher adjusted odds of achieving at least 80% drug adherence across the PMTCT cascade of care, compared to women on short-course ARV prophylaxis (Table 2). During pregnancy, women taking lifelong triple ART had 4.1 times higher adjusted odds of reporting at least 80% adherence, compared to women taking short-course ARV prophylaxis ($p<0.01$). During postpartum, women taking lifelong triple ART had 3.8 times higher adjusted odds of at least 80% adherence, compared to women on the short course prophylaxis ($p<0.01$). Finally, women on the lifelong triple ART regimen had 3.5 times higher adjusted odds of reporting at least 80% adherence to giving the infant NVP prophylaxis compared to women taking short-course ARV prophylaxis regimen ($p=0.001$). No covariates were significantly associated with drug adherence during or after pregnancy in our adjusted models.

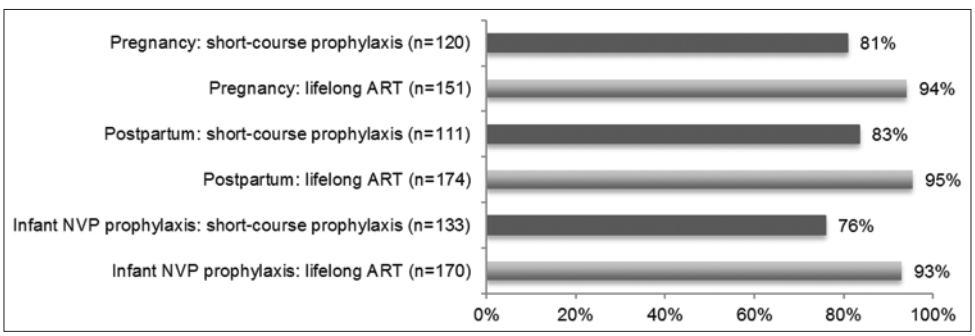

Figure 1: Proportion of participants reporting at least 80% drug adherence during each time period in the PMTCT cascade of care

Table 2: Logistic regression results for the odds of drug adherence across the PMTCT continuum of care by type of regimen and covariates

Variable	>80% Pregnancy adherence (n=271)[1]			>80% Postpartum adherence (n=285)			>80% Infant NVP prophylaxis adherence (n=303)		
	aOR	95% CI	*P*	aOR	95% CI	*P*	aOR	95% CI	*P*
Woman on lifelong triple ART[2]	4.14	1.67-10.28	0.002	3.83	1.43-10.27	0.007	3.46	1.62-7.38	0.001
Age	1.02	0.92-1.12	0.754	1.05	0.94-1.17	0.408	1.03	0.94-1.13	0.541
Infant age	0.98	0.83-1.15	0.799	0.95	0.80-1.13	0.570	0.94	0.82-1.09	0.429
Parity	0.89	0.64-1.24	0.497	0.87	0.60-1.26	0.456	1.01	0.73-1.40	0.944
Gestational age of first ANC visit	0.54	0.25-1.18	0.122	0.45	0.19-1.04	0.061	0.82	0.43-1.55	0.545
Diagnosed during most recent pregnancy[3]	1.30	0.52-3.29	0.574	1.39	0.51-3.79	0.518	0.70	0.30-1.59	0.391
Highest educational attainment	0.87	0.61-1.25	0.457	1.09	0.72-1.67	0.681	1.02	0.74-1.42	0.891
Knowledge of PMTCT	1.54	0.96-2.48	0.076	1.17	0.73-1.87	0.516	1.04	0.71-1.53	0.832
Standardized wealth index score	1.20	0.81-1.78	0.370	1.53	0.97-2.62	0.066	1.28	0.90-1.82	0.167

aOR is adjusting for participant's age, infant age, parity, gestational age at first antenatal ANC visit, whether the woman was diagnosed with HIV during this most recent pregnancy or before, highest educational attainment, knowledge of PMTCT, and wealth, [1]Sample size varies because women were not offered medication consistently across all protocols, [2]Comparison group: woman on short-course ARV prophylaxis, [3]Comparison group: woman diagnosed prior to most recent pregnancy

4. Discussion

Women who were eligible for treatment under option A and taking lifelong triple ART had significantly higher adjusted odds of self-reported adherence to medication across the PMTCT cascade of care, compared to women taking short-course ARV prophylaxis. One hypothesis regarding this association is that women taking lifelong triple ART may have known they were HIV positive for longer periods of time due to a more progressed HIV stage, which enabled more time to accept the diagnosis, disclose their status to household members, and be more psychosocially prepared to take ARVs,[25,26] resulting in better adherence. In the present study, whether the woman was diagnosed with HIV during or prior to the most recent pregnancy was not significantly associated with adherence. However, this measure may not have adequately captured enough variability in the duration of time women had been living with HIV to detect a significant relationship. We also, unfortunately, did not have a measure of time on ART for women eligible for lifelong treatment. Future studies capturing both time since diagnosis and time on ART in the form of years and months are needed to show whether the above hypothesis holds true.

Nonetheless, with the adoption of Option B+ in countries such as Zambia,[27] it will be essential to take extra care to ensure newly diagnosed women are able to adjust psychologically with the initiation of lifelong ART from onset of diagnosis. Indeed, research from Malawi – the country with the most experience implementing Option B+ – indicates that health workers have raised concerns about the policy of initiating women on ART the same day they are diagnosed, arguing that newly diagnosed women are not adequately prepared and often need time to psychologically adjust before beginning lifelong ART.[28]

Another plausible explanation for better adherence among women on triple ART compared to short course ARV prophylaxis in this study is that women on lifelong ART may have been symptomatic with HIV-related disease because they were eligible for treatment under Option A. Symptoms related to HIV disease progression may have provided additional motivation among the women in this study to adhere in order to get well.[29,30] Indeed, research from Malawi has indicated that women who initiate triple ART through Option B+ are more likely to be lost to follow-up than women who initiate because of a low CD4 count.[31,32]

Similarly, the messaging to people living with HIV has traditionally explained that some people need to start ART for their own health while others do not.

This may have motivated the pregnant/breastfeeding women in this study on lifelong therapy to be adherent when they were told to start ART. This also points to the need to change the messaging under Option B+ in order insure that all HIV-positive pregnant or breastfeeding women know they need to start ART and have high long-term adherence for both PMTCT and their own health beyond the peripartum period.

The findings of this study run contrary to a meta-analysis that found mothers on prophylaxis had better adherence than mothers on treatment.[12] Several factors may account for our differing findings. First, the meta-analysis included studies from low, middle, and high-income countries, the majority of which were based in the United States. Additionally, the authors reported on various ARV regimens,[12] many of which are not comparable to those in the present article, such as sdNVP or short course AZT alone.

Large differences in adherence to giving the infant NVP prophylaxis between women on lifelong triple ART and short-course ARV prophylaxis were especially noteworthy in the present study, which may be a result of the length of time infant NVP is required. For women on lifelong ART, infant NVP prophylaxis is only indicated for six weeks postpartum. The lifelong triple ART regimen may enable higher adherence to giving infant NVP because HIV-positive mothers find it easier to take medication long-term than give infant medication. In support of this hypothesis, a study from Tanzania found that mothers preferred to take medication themselves postpartum rather than give medication to the infant for extended periods of time.[30]

5. Conclusions and Global Health Implications

We found that women taking lifelong ART were more likely to be adherent across the PMTCT cascade of care compared to women taking short-course prophylaxis. This has important implications moving forward for national PMTCT programing in Zambia and other sub-Saharan Africa settings. Zambia, like many countries in the region, is transitioning to Option B+ where all HIV-positive pregnant and breastfeeding women will initiate lifelong triple ART. Maternal ARV drug adherence is a key factor in the goal towards the elimination of mother-to-child transmission of HIV and improving the health of women living with HIV. The results of this study indicate that lifelong triple ART may in fact promote better ARV drug adherence during and after pregnancy. However, the reasons for improved adherence among women on lifelong ART under Option A may be different than for women initiating under Option B+. There is a critical need for additional studies on adherence as well as for appropriate framing of health messages and psychosocial support for newly diagnosed women in order to support optimal adherence outcomes under the new policy.

This study has several limitations. First, data were collected using retrospective self-reporting, which is vulnerable to recall and social desirability biases. In addition, this was a non-representative clinic-based sample in a low socioeconomic area and is likely not generalizable to rural or higher-income African populations. We also were unable to collect data on the differences in mother-to-child transmission rates due to slow turn-around time of pediatric HIV tests at the facility. Lastly, the survey did not include a measure of time on ART or time from diagnosis. Despite these limitations, this study adds valuable insight on ARV adherence during and after pregnancy and is unique in its ability to capture the adherence levels of women on two separate drug regimens within the same population under Option A.

Compliance with Ethical Standards

Conflict of Interest: *The authors declare that they have no conflicts of interest.* ***Ethical Approval:*** *The research protocol was approved by the Colorado Multiple Institutional Review Board and the Excellence in Research Ethics and Science Converge IRB in Lusaka, Zambia.* ***Consent:*** *Written informed consent or a thumbprint was obtained from all participants.*
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Key Messages

- HIV-positive women's adherence to antiretroviral medication during and after pregnancy, including giving the infant prophylaxis, is critical for optimal maternal and child health outcomes.
- Under prevention of mother-to-child transmission (PMTCT) programmatic Option A in Zambia, women taking lifelong antiretroviral therapy report better adherence during and after pregnancy compared to women who were ineligible for treatment and taking short-course prophylaxis.
- The lifelong therapy regimen may be easier for women to follow, particularly giving the infant prophylaxis.

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