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Prevention of Mother-to-Child HIV Transmission: Predictors of Utilization
& Future Policy Implications

By

Tyler Elizabeth Martz

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requirements for the degree of

Doctor of Public Health

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

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Abstract

Prevention of Mother-to-Child HIV Transmission: Predictors of Utilization & Future Policy Implications

by

Tyler Elizabeth Martz

Doctor of Public Health

University of California, Berkeley

Professor Stefano M. Bertozzi, Chair

Despite the availability of highly efficacious antiretroviral drug regimens for the prevention of mother-to-child HIV transmission (PMTCT), transmission rates remain higher than those achieved in clinical trials. Access to these efficacious drug regimens continues to expand rapidly in countries most affected by HIV. Such expansion is an important first step in dramatically reducing mother-to-child HIV transmission rates. However, beyond access to drug regimens, programs must also identify and address individual and structural factors impeding the utilization of and adherence to PMTCT services by the women they are designed to serve. Additional research into factors both positively or negatively associated with PMTCT service utilization could help improve PMTCT programs to further reduce transmission rates.

Each of the three papers included in this dissertation examined different factors of PMTCT service utilization. The first two papers analyze secondary data from a large-scale impact evaluation of Zimbabwe's PMTCT program. Specifically, the first paper explores the association between costs (service costs, travel time, and transportation costs) and utilization of all recommended PMTCT services. The second paper explores the relationship between the timing of a pregnant woman's HIV-positive diagnosis, either prior to pregnancy or during antenatal care, and her utilization of PMTCT services. The hypothesis was that women who were diagnosed prior to pregnancy, having had more time to cope with their diagnosis, would complete more of the recommended PMTCT services. The final paper utilizes policy analysis methodology to examine two different implementation strategies Malawi could consider to improve lifelong adherence to antiretroviral therapy (ART) among women living with HIV who initiate treatment during pregnancy or breastfeeding. The two strategies proposed were: 1) for all pregnant/breastfeeding women to initiate and indefinitely receive treatment at maternal and child health clinics rather than be transferred to an ART specialty clinic, and 2) to expand access to lifelong ART, regardless of stage of disease, to any individual living with HIV in the pregnant/breastfeeding woman's household.

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Introduction

Although pediatric HIV infections are preventable, 240,000 children were newly infected with HIV globally in 2013.¹ Once infected, less than half of these children will survive long enough to reach two years of age.^{2,3} With an estimated 1.3 million women living with HIV giving birth each year, 85% of whom are in sub-Saharan Africa, prevention is paramount.¹ Available prophylactic treatments for the prevention of mother-to-child HIV transmission (PMTCT) can reduce transmission rates of 25-35% to less than 5% in breastfeeding populations.⁴ Global mother-to-child transmission rates, however, were last estimated to be 16%.⁵ Additional effort must be made to determine how to reduce transmission rates further.

PMTCT Drug Regimens

Countries around the world currently are scaling up the World Health Organization's (WHO) 2013 PMTCT treatment guidelines. These guidelines require HIV-positive pregnant women to adhere to combination antiretroviral regimens from 14 weeks gestation until the cessation of breastfeeding, if not for the rest of their lives.⁶ These new regimens are a dramatic shift from single-dose or short-course regimens employed previously in many countries.

Clinical trial data first demonstrated the efficacy of antiretroviral drugs for PMTCT in 1994.⁷ Widespread utilization of antiretroviral drugs for PMTCT in developing countries occurred in the early 2000s, and largely involved the administration of a single-dose of Nevirapine to pregnant women at the onset of labor.⁸ In 2004, the WHO released new PMTCT treatment guidelines recommending the use of short-course zidovudine (AZT) from 28 weeks gestation, with additional drugs given at labor onset and seven days postpartum.⁹ These guidelines largely went unchanged, and few countries fully operationalize these recommendations, until 2010 when the WHO outlined two new recommendations, Option A and Option B.⁴ Option A provided women not yet qualifying for lifelong antiretroviral therapy (i.e. CD4 count \leq 350 cells/ml) with AZT starting at 14 weeks gestation and single-dose Nevirapine and AZT plus 3TC at delivery through seven days postpartum. Option B placed all women on combination antiretroviral therapy throughout pregnancy and during the duration of breastfeeding. Under both Option A and Option B, those mothers requiring treatment for their own health (i.e. at the treatment threshold of CD4 \leq 350 cells/ml) were placed on lifelong treatment. The latest treatment guidelines were revised in 2013.⁶ These guidelines now preferentially recommend Option B+, which places all HIV-positive pregnant women on lifelong antiretroviral therapy regardless of her stage of disease, and no longer recommend Option A due to its more complicated treatment regimens and dependence on CD4 testing. These WHO guidelines serve as recommendations from which countries can then determine which option (Option B or B+) works best for their particular epidemic context, health care infrastructure, and budgets. However, the selection of the drug regimen option within a country is only one piece to preventing pediatric HIV infections.

PMTCT Service Utilization

As these more efficacious regimens become more available, an increasing proportion of avoidable infections are due to insufficient retention throughout the continuum of PMTCT services. To reduce mother-to-child HIV transmission rates, mother-infant pairs must complete sequential steps of PMTCT services. First, all pregnant women receiving antenatal care must be offered, tested, and receive the results of an HIV test. If HIV-positive, a woman must then receive a CD4 test to determine the appropriate treatment regimen. All guidelines except Option B+ indicate that women with CD4 counts above 350 cells/ml (prior to 2013) or above 500 cells/ml (after 2013), and thus not qualifying for lifelong antiretroviral therapy for her own health, be placed on prophylactic treatment solely for the purposes of PMTCT.^{4,6} These women would, therefore, stop prophylactic treatment once their child was no longer being exposed to maternal antibodies and would not resume treatment until their next pregnancy or until their CD4 count reached the treatment threshold. While some countries will continue to follow these guidelines, most countries are adopting Option B+, which will place all HIV-positive pregnant women on lifelong ART, regardless of their CD4 count. This shift will eliminate the step pertaining to obtaining a CD4 test, and by doing so hopefully retain more women in PMTCT care. Next, once on the indicated treatment, women must adhere to the indicated treatment regimens, in addition to ensuring their infants also ingest their prophylactic doses as prescribed. The final step requires all HIV-exposed infants to receive an HIV test, and if HIV-positive, be initiated on treatment to improve their survival probability. Therefore, each distinct step plays an important role in preventing or identifying pediatric infections; failure to complete any step limits the effectiveness of PMTCT programming. For example, Barker *et al* modeled that mother-to-child HIV transmission rates could be reduced from 19.7% to 7.9% simply by ensuring that 95% of mother-infant pairs complete all of the PMTCT services.¹⁰ A better understanding of the factors that limit women's utilization of services or retention throughout the continuum of services could help future programming to adapt to reduce these barriers.

Despite the importance of completing each service step, non-adherence and attrition are noted problems and translate into higher transmission rates. For example, in 2013, in the 21 countries with the highest HIV prevalence among pregnant women, 68% of pregnant women living with HIV received antiretroviral drugs, but only 39% of HIV-exposed infants received an HIV-test within two months of delivery.⁵ Additionally, non-adherence to treatment continues to be an issue. When treatment regimens required mother-infant pairs to ingest only single-doses of Nevirapine, one study found only 54% adherence.¹¹ In Malawi, following the implementation of Option B+, by twelve months only 77% of women were reported to be retained on treatment.¹² Further, Myer *et al* found that pregnant women were significantly more likely to be lost to follow up than non-pregnant women when initiated on combination antiretroviral therapy regimens similar to those included in the current WHO guidelines (19% vs. 11%).¹³ Such attrition limits the effectiveness of PMTCT programs.

There are a number of factors reported to be associated with PMTCT service utilization. Known barriers to PMTCT service utilization and adherence include non-disclosure of status to a sexual partner or family members,^{14,15,16,17} long wait times at clinics,^{14,18} and no male partner involvement.^{19,20} Service costs and transportation time and cost are also cited reasons for why

women do not utilize PMTCT services.^{14,21,22,23,24,25} Other factors shown to be associated with increased PMTCT service utilization include increased maternal age,^{26,27,28} and higher educational attainment.^{29,15} Experience with PMTCT programs in a previous pregnancy has also been shown to increase adherence to drug regimens in later pregnancies.^{15,30} Gaining a better understanding of additional factors that might be affecting PMTCT utilization should be explored to help improve adherence to PMTCT services.

Overview of the dissertation

Each of the three papers included in this dissertation examined different factors of PMTCT service utilization. The first two papers analyze secondary data from a large-scale impact evaluation of Zimbabwe's PMTCT program. Specifically, the first paper explores the association between costs (service costs, travel time, and transportation costs) and utilization of all recommended PMTCT services. The second paper explores the relationship between the timing of a pregnant woman's HIV-positive diagnosis, either prior to pregnancy or during antenatal care, and her utilization of PMTCT services. The hypothesis was that women who were diagnosed prior to pregnancy, having had more time to cope with their diagnosis, would complete more of the recommended PMTCT services. The final paper utilizes policy analysis methodology to examine two different implementation strategies Malawi could consider to improve lifelong adherence to antiretroviral therapy (ART) among women living with HIV who initiate treatment during pregnancy or breastfeeding. The two strategies proposed were: 1) for all pregnant/breastfeeding women to initiate and indefinitely receive treatment at maternal and child health clinics rather than be transferred to an ART specialty clinic, and 2) to expand access to lifelong ART, regardless of stage of disease, to any individual living with HIV in the pregnant/breastfeeding woman's household.

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Paper 1: The role of service costs, transportation costs and travel time in the utilization of prevention of mother-to-child HIV transmission services in Zimbabwe

Abstract

Objective: We explored the association between service costs, transportation time, and transportation costs and complete utilization of all recommended PMTCT services.

Methods: We utilized data from two serial cross-sectional surveys in 2012 and 2014 in the catchment areas of 157 health facilities located across 5 provinces in Zimbabwe. Our sample included 1939 mothers living with HIV who were ≥ 16 years of age with infants born 9-18 months prior to the survey dates. We generated a dichotomous outcome variable to capture receipt of all of the following: 4 antenatal care (ANC) visits, CD4 test and its result, facility delivery, maternal antiretroviral drugs (ARVs), infant ARVs, and an infant HIV test. We then utilized logistic regression to explore the association between service costs, transportation time, and transportation costs and complete service utilization.

Results: Overall, 36% of women completed all six of the services examined. Average round-trip transportation time was 1.6 hours (SE 0.1). Average round-trip transportation costs were US\$1.73 (SE 0.2), however, 58% of our sample reported paying nothing for transportation. For all services, except for ANC and a facility delivery, at least 98% of our sample reported paying nothing to the health facility for service utilization. In the multivariate model, for each hour increase in round-trip transportation time there was a 12% decrease in the odds of complete service utilization (95% CI: 0.81-0.95), adjusting for socio-demographic factors and survey round. We found no association between transportation cost and complete service utilization (OR: 0.99, 95% CI: 0.98-1.01) or total average package costs and complete service utilization (OR 1.00, 95% CI 0.999-1.00).

Conclusion: Reducing travel time to health facilities may help improve utilization of all recommended PMTCT services.

Introduction

In 2013, an estimated 1.3 million women living with HIV gave birth.¹ Current antiretroviral (ARV) regimens for the prevention of mother-to-child HIV transmission (PMTCT) can reduce transmission rates to below 5%, compared to 25-35% in the absence of any intervention.² The increased availability of more efficacious PMTCT drug regimens and global efforts to reduce new pediatric HIV infections by 90% of 2010 levels by 2015,^{3,4} have resulted in noticeable declines in transmission rates. Between 2009 and 2013, the number of new pediatric infections in the 22 countries with the highest HIV-prevalence among pregnant women decreased by 43%.⁵ Although significant progress has been made, mother-to-child transmission rates were last estimated to be 16%.⁵ Therefore, additional work needs to be done to reduce transmission rates to below 5%. The identification of barriers to uptake of PMTCT services faced by pregnant women living with HIV could inform future program operations to help reduce these barriers, and ultimately transmission rates, going forward.

In addition to being placed on an effective drug regimen, there are a number of other services pregnant women living with HIV should receive to improve maternal and child health outcomes. The World Health Organization recommends that all pregnant women should attend at least four antenatal care (ANC) visits and deliver in a health facility to improve maternal health outcomes.^{6,7} This is especially important for women living with HIV, as they have a higher maternal mortality rate compared to HIV-uninfected mothers.^{8,9} Pregnant women living with HIV should also receive a CD4 test and its result to determine if they should be placed on antiretroviral drugs (ARVs) solely for PMTCT prophylaxis purposes or on lifelong, combination antiretroviral therapy (ART) to reduce their HIV-related morbidity and mortality.¹⁰ In addition to adhering to the prescribed treatment regimen, mothers must also ensure they receive and administer infant prophylactic doses of ARVs. Finally, all HIV-exposed infants should receive an HIV-test to determine their HIV-status.

There are a number of factors that reduce the likelihood of PMTCT service utilization. Known barriers to PMTCT service utilization and adherence include non-disclosure of status to a sexual partner or family members,^{11,12,13,14} long wait times,^{11,15} and no male partner involvement.^{16,17} Service costs and transportation time and cost are also cited reasons for why women do not utilize PMTCT services. Beyond the actual cost and time it takes for women to access services, these factors are likely barriers because the decision to travel or to use their resources to pay for a service takes them away from their other competing demands like child rearing, subsistence or employment activities, or other household responsibilities. Previous studies qualitatively referenced or reported the frequency with which distance or costs were reportedly factors in decisions not to utilize particular services.^{11,18,19,20,21,22} However, how costs and travel time are associated with the utilization of all of the recommended PMTCT services has not been examined closely and with a large sample of women living with HIV.

The objective the current study was to determine the association between service costs, transportation time, and transportation costs and complete utilization of all recommended PMTCT services among a sample of women living with HIV in Zimbabwe. Within Zimbabwe, HIV prevalence among women 15-49 years of age is 18% and the average fertility rate is 4.1 children.²³ This high burden of HIV infection among women places Zimbabwe on the list of the 22 priority countries for *elimination* (defined by this initiative as the reduction in pediatric infections by 90% of 2009 levels) of pediatric infections by 2015.³ Exploration of factors affecting utilization of PMTCT services within this country context could inform their programming going forward.

Methods

For this study, we utilized survey data collected for the impact evaluation of Zimbabwe's national PMTCT program. Two rounds of serial cross-sectional survey data were collected, in 2012 and 2014, to measure the impact of their accelerated PMTCT program on mother-to-child HIV transmission rates and HIV-free infant survival. A major component of the accelerated program was the implementation of Option A of the World Health Organization's 2010 treatment guidelines. Option A placed pregnant women whose CD4 count was above 350

cells/ml on azidothymidine (AZT) starting at 14 weeks gestation and postpartum AZT or nevirapine prophylaxis for infants depending on their breastfeeding status.¹⁰ Pregnant women whose CD4 count was below 350 cells/ml were placed on lifelong ART.

Study Population & Sampling Strategy

We randomly sampled mother-infant pairs with biological mothers or caregivers 16 years of age or older who had infants born 9-18 months prior to the survey from the catchment areas of 157 randomly sampled health facilities in 5 of 10 provinces in Zimbabwe. Specifically, we purposively selected provinces (Harare, Manicaland, Mashonaland Central, Mashonaland West, and Matabeleland South) to include major cities; heterogeneity in HIV-prevalence and presence of electronic medical record systems; and geographic and ethnic diversity. Health facilities within the selected provinces were randomly sampled from the 699 health facilities offering PMTCT services. Village health workers, infant immunization registries, and village heads within the health facility catchment areas were employed to enumerate households with an infant born in the two years prior to the survey. Households on these lists were then screened for eligible mother/caregiver-infant pairs. Using a predetermined sampling fraction for each catchment area, eligible pairs were randomly selected to participate in the survey. Overall, a total of 19,721 biological mothers and caregivers, over the two survey rounds, consented to participate in the questionnaire.

For this analysis, we first restricted the sample to include only biological mothers with a self-reported HIV-positive test result (n=2093). We then excluded 49 women who reported learning of their HIV-positive status at delivery, as these women would not have known their status during the earlier service utilization steps under examination. We further excluded 105 women from the analysis for whom there was a missing response regarding whether they had received a CD4 test, 102 of whom were diagnosed prior to pregnancy. Therefore our final weighted sample included 1938.97 mothers (based on 1939 observations) diagnosed prior to or during ANC of the eligible pregnancy. A weighted sample is used for all analyses to account for the multi-stage sampling strategy and the correlated nature of data within health facility catchment areas. No study variable had more than 0.46% missing values.

Data Collection

We conducted the two cross-sectional surveys in April-September 2012 and July-December 2014. We sought informed consent from all randomly selected mothers, and once obtained, mothers then completed an interviewer-administered questionnaire. We recorded all responses on handheld digital devices without the collection of any personal identifiers to ensure complete anonymity of the study participants. The questionnaire collected information on ANC and PMTCT service utilization, associated service utilization costs, transportation time, and transportation costs, as well as household and individual socio-demographic characteristics.

Analysis

We calculated frequencies of socio-demographic characteristics and service utilization. We generated a dichotomous outcome variable that captured complete service utilization.

Complete utilization, therefore, required a woman to have completed at least four ANC visits (yes/no), received a CD4 test and its result (yes/no), delivered in a health facility (yes/no), received maternal ARVs (yes/no), received infant ARVs (yes/no), and received an infant HIV test (yes/no). Our exposure variables were self-reported service costs associated with utilization of each service, and round-trip transportation time and transportation costs to the health facility.

All service utilization costs are the self-reported costs the individual reported paying and not the costs health facilities reported charging for services. To determine service costs, we generated the average price paid per service per health facility catchment area in the assumption that women in the same catchment area would face similar prices. Although some mothers may have sought services at more than one clinic, all prices were assigned to the sampled clinic around which the sample was selected. In those instances where a woman indicated that she paid a flat consultation fee that covered multiple services, we divided it proportionally across the services under examination. Specifically, to proportionally distribute the flat consultation fee to specific services we first calculated the average price paid for each service, among those who paid something, within each health facility catchment area. We then summed up the price of each of the services to obtain the total package price (for the six services under examination) per catchment area. We then determined the proportion that each service contributed to the total package per catchment area. We then used that proportion to attribute the corresponding amount of the flat consultation fee to each of the services the mother reported were covered by her flat consultation fee. These prices were then added to the average service costs of the catchment area, which includes both individuals who paid for services and those women who accessed services for zero cost. We then totaled the average service cost of each of the individual services per catchment area to get the total average package cost of utilization of all six services per catchment area.

We calculated the average round-trip transportation time and transportation costs to the health facility. In instances where a woman reported utilizing services across a number of different facilities, the total transportation time and costs were averaged across the different facilities. Although the questionnaires asked women to report transportation time in minutes one-way to the facility to ease their estimation, we doubled these responses to capture round-trip transportation time. We further adjusted transportation time from minutes to hours. All costs are reported in US dollars. Although the US dollar is the official currency in Zimbabwe, the questionnaire allowed women to report costs in South African Rand, another commonly used currency in the country. In those instances where women reported costs in South African Rand we converted the responses to US dollars using the conversion rate at start of each survey round: 7.8 and 10.7 Rand per US dollar in April 2012 and July 2014 respectively.²⁴

We used logistic regression to conduct bivariate and multivariate analyses. Covariates included maternal age, parity, educational attainment, marital status, household size, religion, province, a proxy wealth variable, and survey year (see Table 1 for variable categories). We conducted a polychoric principal component analysis on variables capturing household assets, building materials, water source, and toilet facility to create a proxy wealth index variable. We then divided the index into quarters. We used Stata 13 (Stata Corporation, College Station, Texas).

We examined variance inflation factors and correlation matrices to determine any issues with multicollinearity, for which we found no violations. We tested for interactions between survey year and our two cost variables (total package costs and transportation costs), as we thought the relationship between complete utilization and those variables might be different by survey year. We found no significant interaction and therefore did not include interaction terms for those variables in our model.

Human Subjects

The Medical Research Council of Zimbabwe, and the Institutional Review Boards at the University of California, Berkeley and University College London reviewed and approved the study materials and protocol prior to implementation.

Results

The weighted population of mothers living with HIV had an average age of 29.6 years, 63% lived in a rural catchment area, 84% were currently married, and mean household size was 5.1 inhabitants (**Table 1**). Overall utilization of each service step was high. 98% of mothers reported utilizing antenatal care in a health facility at least once during their pregnancy, with 74% attending four or more ANC visits during their eligible pregnancy. While only 58% of mothers received a CD4 test and the result of that test, 86% of mothers delivered in a health facility or on the way to the facility, and 79% and 78% reported receiving maternal ARVs and infant ARVs, respectively. (**Table 2**) Overall, 34% of mothers completed all six of the steps examined, 28% completed 5 of the steps, 13% completed 4 steps, and 24% completed 3 or fewer steps.

Service Costs, Transportation Time, Transportation Costs

Average round-trip transportation time was 1.6 hours, and average round-trip transportation costs were US\$1.73. Fifty-eight percent of our sample reported paying nothing for transportation cost. Additionally, we found a high percentage of individuals who reported not having to pay anything to the health facility for each of the services utilized. Specifically, the percentage of our sample who reported paying nothing for service utilization was as follows: 56% for ANC visits, 98% for CD4 test, 69% for a health facility delivery, 99% for maternal ARVs, 99% for infant ARVs, and 100% for an infant HIV test. Overall, 47% of women paid nothing for utilization of all services. Although women who paid nothing to access the services make up a large proportion of the sample and were included in the average service costs per catchment area, the overall mean total package cost was US\$ 60.25.

In bivariate analysis, each hour increase in round trip transportation time was associated with a 13% decrease in the odds of complete service utilization (OR 0.87, 95% CI: 0.79-0.95). We found no association between round trip transportation costs and complete service utilization (OR 0.99, 95% CI: 0.97-1.00) or between the total average package cost and complete service utilization (OR 1.00, 95% CI: 0.998-1.00). Additionally, we examined if the average service costs per catchment area for ANC and health facility delivery, the two services with 44% and 31% non-zero payments respectively, were associated with complete service utilization in bivariate logistic regression analysis. We thought that some of the other services offered during those

key health visits could have been subsumed in the costs paid. We found no association for either ANC or facility delivery service costs with complete service utilization, and therefore, did not include either in the final model. (Data not shown)

After adjusting for the other covariates, the relationships of the three main exposure variables and complete service utilization remained the same. In the multivariate model, for each hour increase in transportation time there was a 12% decrease in the odds of complete service utilization (95% CI: 0.81-0.95). (**Table 3**) Although each dollar increase in transportation costs was slightly negatively associated with decreased odds of complete service utilization, the association was not significant (OR: 0.995, 95% CI: 0.98-1.01). Finally, no association between the average package cost and complete service utilization persisted in the multivariate model (OR 1.00, 95% CI 0.999-1.00).

Other factors significantly associated with complete service utilization

In the adjusted model, factors positively associated with increased odds of complete service utilization include increased maternal age (OR: 1.06, 95% CI: 1.03-1.09), a 2014 survey round (OR: 3.36, 95% CI: 2.61-4.34), and residing in a province other than Harare. Specifically, residents of Manicaland province had 2.75 times the odds (95% CI: 1.41-5.33), Mashonaland Central province had 2.82 times the odds (95% CI: 1.52-5.23), Mashonaland West province had 2.50 times the odds (95% CI: 1.28-4.85), and Matabeleland South province had 3.32 times the odds (95% CI: 1.74-6.35) of complete service utilization compared to residents of Harare.

Discussion

In this study, we explored the role service costs, transportation time, and transportation costs played in utilization of key PTMCT services. We found that nearly all women paid nothing to receive four of the services (CD4 test, maternal and infant ARVs, and an infant HIV test), but paying for ANC and delivery services remained relatively common. Contrary to expectation, we found no association between total package service costs and complete service utilization. We observed a negative association between each hour increase in transportation time and complete service utilization, but found no association between transportation costs and complete service utilization.

In Zimbabwe, pregnant women and children under five years of age are exempt from service costs, and all ARV treatment is supposed to be provided without cost.²⁸ However, previous evidence suggested that the charging of informal fees was still a practice at some clinics to cover basic operating costs.²⁸ Although 47% of women in our sample reported no service costs, we thought it might be possible that the costs paid to access ANC or a health facility delivery covered the costs of the other services. We believed this might explain why the percentage of women reportedly paying a non-zero price for ANC and delivery remained much higher compared to the other services. However, when we examined the relationship between these costs and complete service utilization in bivariate analyses, we found no association. Although there was no association between these two service costs and complete utilization, we still felt it important to include the total average package cost in the final model to control for service

costs. Further, the fact that the four other services had reported service utilization costs of zero for all women in 98% or higher of cases is a testament to how effectively the policy regarding free service utilization for pregnant women living with HIV has been implemented. This finding is consistent with evidence from other studies indicating that the removal of user-fees increased service utilization.^{29,30,31,32,33} The fact that service utilization levels were relatively high, even in the presence of utilization costs for ANC and delivery, may either be an indication that service utilization is not especially price sensitive at current prices or an indication that the facilities are selectively imposing fees on those women with sufficient ability to pay. However, the available data did not permit us to know why some women paid for services while others did not.

The study's power to detect an association between transportation costs and service utilization was lower than for travel time given that most women likely walked to the clinic and did not incur any out-of-pocket costs. However, there was not even the suggestion of an important association. In contrast, we found that increased travel time was significantly associated with decreased likelihood of complete service utilization. This finding is similar to other studies which found that greater distance to the facility was a barrier to service utilization.^{34,18,19,21, 35} However, the quantification of the association between travel time and complete utilization of all recommended PMTCT services among such a large sample of women living with HIV has not been conducted previously.

Utilization of each of the services examined was above 72%, with the exception of receiving a CD4 test and the result. The utilization levels of each of the services are comparable to reported utilization levels in other countries.^{25,26,27} Further, 34% of women in our sample utilized all six of the WHO recommended services. A study in South Africa examining uptake of HIV testing, CD4 testing and a result, maternal ARV/ART, and infant ARVs found that 65% of mothers living with HIV utilized all four of those steps.²⁶ The inclusion of knowledge of their HIV-status, which tends to be high since opt-out HIV-testing in ANC was adopted, and the higher reported uptake of CD4 testing and its result, likely explains the higher reported utilization of all services than what we found, though the exact services examined in the two studies differ slightly.

It is not surprising that increased maternal age was associated with increased odds of complete service utilization, as this finding is consistent with other studies.^{36,37,38} Additionally, given that between the two survey rounds, Zimbabwe scaled-up access to more efficacious drug regimens and other program improvements (including access to point-of-care CD4 machines),^{39,40,41,3} it is not unexpected that a 2014 survey round was associated with increased odds of complete service utilization. Interestingly, residing in provinces other than Harare, the capital, resulted in greater than double the likelihood of complete service utilization. It is possible that the health clinics in Harare were larger and potentially more crowded than the sampled clinics in other provinces, which could have deterred individuals from completing all of the services.

There are a number of limitations of this study. For example, all data are self-reported and mothers were asked to recall expenditures and travel time that occurred 9-18 months prior to the survey. Therefore, inaccurate recall, either in the form of over or underestimation of the

associated costs or travel time, is a possibility. However, if the participants frequently use these same clinics for other health services then travel time and transportation costs might be fairly accurately recalled. Additionally, given previously reported differences between the costs facilities report charging and the costs participants report paying,⁴² we were unable to utilize standardized, health facility reported costs for each service step. Our inability to account for any complications associated with a woman's pregnancy might also be a factor in the reported service costs and subsequent service utilization, with women experiencing complications likely having to pay more than women without complications. Further, we made the assumption that the reported one-way travel time would simply be doubled to capture a round-trip estimate. However, it is possible that some variability might exist in modes of transport or in duration of travel to and from the clinics.

While we observe relatively high service utilization levels among this population of mothers living with HIV, transportation time remains a barrier to even greater levels of service utilization. Potential opportunities for removing this barrier would be to increase the use of mobile clinics to bring services closer to each village or to increase the number of health facilities providing PMTCT service to reduce the distance covered by each facility. Additionally, the fact that nearly all pregnant women paid nothing for all services, with the exception of antenatal care and delivery, illustrates how the use of informal fees previously reported is relatively small. As Zimbabwe continues to make tremendous strides at increasing access and utilization of prevention of mother-to-child HIV transmission services, continued efforts will be needed to further minimize barriers.

Table 1: Demographic Characteristics of HIV+ women with 9-18 month year olds in Zimbabwe

Characteristic	N	(%)
Total	1939.0	100.0
Education		
Primary or less	612.1	31.6
Forms 1-3	592.4	30.6
Form 4	686.4	35.4
Form 5+	48.0	2.5
Marital Status		
Not Married	304.5	15.7
Currently Married	1632.0	84.3
Urban/Rural		
Rural	1212.0	62.5
Urban	726.6	37.5
Province		
Harare	478.8	24.7
Manicaland	582.1	30.0
Mashonaland Central	292.7	15.1
Mashonaland West	294.0	15.2
Matabeleland South	291.4	15.0
Religion		
Roman Catholic	119.0	6.1
Apostolic	620.4	32.0
Pentacostal	415.4	21.5
Other	539.1	27.8
No religion	242.9	12.5
Wealth Index (quarters)		
1	419.9	21.7
2	365.9	18.9
3	461.0	23.8
4	690.0	35.6
Survey Year		
2012	933.1	48.1
2014	1006	51.9
Age, years (Mean, SE)	29.6	0.2
Household Size (Mean, SE)	5.1	0.1
Parity (Mean, SE)	3.1	0.1

Table 2: PMTCT Service Utilization & Average Total Package Costs, Transportation Time, Transportation Costs (N=1939)

Service	N	(%)
4+ ANC visits		
No	497.9	25.7
Yes	1441.0	74.3
Facility Delivery		
No	268.2	13.8
Yes	1671.0	86.2
CD4 test & result		
No	818.4	42.2
Yes	1121.0	57.8
Maternal ARVs		
No	413.5	21.3
Yes	1525.0	78.7
Infant ARVs		
No	427.9	22.1
Yes	1511.0	77.9
Infant HIV test		
No	542.5	28.0
Yes	1393.0	72.0
Total Number of Steps Utilized		
0	17.8	0.9
1	111.8	5.8
2	220.0	11.4
3	122.8	6.3
4	258.2	13.3
5	541.5	27.9
6	666.9	34.4
Average Roundtrip Transportation time (Mean hours SE)		
	1.6	0.1
Average Roundtrip Transportation Cost (Mean US\$, SE)		
	1.7	0.2
Total Average Package Cost (Mean US\$, SE)		
	60.3	14.0

Table 3: Adjusted Model Examining the Association between Service Costs, Transportation Costs and Travel Time and Complete Service Utilization (N=1924.5)

	Odds Ratio	P-Value	[95% CI]
Total Average Package Cost (US\$)	1.00	0.31	[1.00,1.00]
Average Transportation Cost (Roundtrip, US\$)	0.995	0.52	[0.98,1.01]
Average Transportation time (Roundtrip, per hour)	0.88**	0.00	[0.81,0.95]
Maternal Age	1.06***	0.00	[1.03,1.09]
Education			
Primary or less (reference)			
Form 1-3 Education	1.08	0.55	[0.83,1.40]
Form 4 Education	1.51*	0.02	[1.08,2.10]
Form 5+ Education	1.26	0.67	[0.44,3.59]
Parity	0.93	0.36	[0.81,1.08]
Currently married	1.19	0.34	[0.83,1.69]
Household Size	0.94	0.13	[0.86,1.02]
Religion			
Roman Catholic (reference)			
Apostolic Religion	0.88	0.61	[0.53,1.45]
Pentacostal Religion	1.24	0.39	[0.76,2.02]
Other Religion	1.01	0.96	[0.62,1.67]
No Religion	0.76	0.40	[0.41,1.43]
Wealth Index (quarters)			
Wealth Index 1 (reference)			
Wealth Index 2	0.87	0.46	[0.60,1.26]
Wealth Index 3	0.94	0.72	[0.65,1.34]
Wealth Index 4	1.26	0.21	[0.88,1.80]
Province			
Harare (reference)			
Manicaland Province	2.75**	0.00	[1.41,5.33]
Mashonaland Central Province	2.82**	0.00	[1.52,5.23]
Mashonaland West Province	2.50**	0.01	[1.28,4.85]
Matabeleland South Province	3.32***	0.00	[1.74,6.35]
Survey Round			
2012 (reference)			
2014	3.36***	0.00	[2.61,4.34]

* p<0.05, ** p<0.01, *** p<0.001

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Paper 2: Timing of maternal HIV-diagnosis and utilization of prevention of mother-to-child HIV transmission services in Zimbabwe

Abstract

Objective: We explored the relationship between the timing of a pregnant woman's HIV-positive diagnosis, either prior to pregnancy or during antenatal care (ANC), and her utilization of prevention of mother-to-child HIV transmission (PMTCT) services.

Methods: We utilized serial cross-sectional data from the 2012 and 2014 impact evaluation surveys of Zimbabwe's national PMTCT program. Our analysis sample included mother-infant pairs with an infant born 9-18 months prior to the survey and a mother ≥ 16 years with a self-reported HIV-positive diagnosis prior to or during ANC of the eligible pregnancy. We explored the self-reported receipt of: a CD4 test, maternal antiretroviral drugs (ARV), infant ARVs, and an infant HIV test. Using multinomial logistic regression, we examined the relationship between timing of diagnosis and three distinct levels of service utilization: zero, some, and all.

Results: We included 1939 mothers in our analysis; 965 diagnosed prior to pregnancy and 974 diagnosed during ANC. We observed important shifts in service utilization between the two diagnosis categories between 2012 and 2014, where utilization of each service was much lower for women diagnosed prior to pregnancy compared to women diagnosed during ANC in 2012, but reversed and was much higher in 2014. We report stratified results given the presence of significant interaction between survey year and diagnosis timing (p -value for interaction < 0.001). In 2012, mothers diagnosed during ANC were more likely to utilize some compared to zero services (OR_a 15.02, 95% CI: 7.86, 28.70) and all compared to zero services (OR_a 13.25, 95% CI: 6.30, 27.87), independent of sociodemographic and pregnancy intention factors. In 2014, however, diagnosis during ANC reduced the odds of utilizing some compared to zero services (OR_a 0.26, 95% CI: 0.11, 0.64) and all compared to zero services (OR_a 0.36, 95% CI: 0.16, 0.79).

Conclusion: Understanding how the timing of diagnosis is associated with PMTCT service utilization in later pregnancies could have important implications for future programing.

Introduction

Pregnant women identified as living with HIV must complete a number of steps to reduce the probability of transmitting HIV to their infants and to determine the infants' HIV-status. These steps include the receipt of: a CD4+ T-lymphocyte cell count test to determine the appropriate treatment regimen (for sites not implementing Option B+, which places all pregnant women on lifelong antiretroviral therapy (ART) regardless of stage of disease); maternal antiretroviral prophylaxis (ARV) or combination ART; prophylactic doses of ARVs for HIV-exposed infants during post-natal or breastfeeding periods; and finally, an HIV test for HIV-exposed infants.¹ Each of these steps plays a crucial role in both preventing pediatric infections and in the early detection of those instances where transmission did occur.

While access to and utilization of prevention of mother-to-child HIV transmission (PMTCT) services has increased, retention of pregnant women in PMTCT programs remains a

challenge.^{2,3} The proportion of pregnant women living with HIV who received antiretroviral drugs for PMTCT in 21 priority countries increased from 33% in 2009 to 68% in 2013.⁴ However, only 39% of HIV-exposed infants in priority countries received an HIV-test within two months of delivery in 2013.⁴ Although mother-to-child transmission rates have declined from 29% to 16% over this period,⁴ understanding factors that might contribute to retention could help to further improve PMTCT outcomes.

Several factors have been shown to be associated with increased PMTCT service adherence, including increased maternal age,^{5,6,7} higher educational attainment,^{8,9} and disclosure of one's HIV status to a partner or family member.^{9,10,6} For example, one study in Tanzania found that women younger than 23 years of age had 5.8 times the odds of declining ARVs prior to delivery than older women.⁶ A factor that has not been examined closely is how the timing of a woman's HIV-positive diagnosis relative to her pregnancy (whether prior to or during her pregnancy) might be associated with PMTCT service utilization.

There are a number of indicators that suggest timing might be an important factor in PMTCT service utilization. First, the timing of an HIV-positive diagnosis influences the amount of time a woman has to comprehend her own diagnosis, as well as to disclose her status to others, a factor found to increase adherence to PMTCT treatment regimens.^{9,10,6} Second, studies have found that women with experience with PMTCT programs in a previous pregnancy were more adherent to drug regimens in later pregnancies.^{9,11} Other evidence suggests that women testing HIV-negative or of unknown HIV-status during previous pregnancies may not utilize antenatal care (ANC) during later pregnancies,^{12,13} and therefore, will not enter into PMTCT services at all. If these women seroconverted since their last pregnancy they may only learn of an HIV-positive diagnosis upon delivering in a health facility, if at all. Finally, only one study, Technau et al (2014), has examined explicitly the association between timing of diagnosis and PMTCT service utilization. Their sample, limited to 298 mother-infant pairs with a recently diagnosed HIV-infected infant, found that mothers aware of their HIV-status prior to pregnancy were more likely to receive ARVs and to have their infants tested for HIV earlier.¹⁴ Over time, the proportion of HIV-positive women with a prior HIV-positive diagnosis will increase, as will the proportion of women on treatment prior to becoming pregnant. The different levels of experience of women diagnosed prior to or during pregnancy, both in coping with their HIV-positive diagnosis and their experience accessing PMTCT services, might influence their utilization of services in each of their pregnancies. Although there seems to be many indications that timing of diagnosis could play an important role in PMTCT service utilization, the examination of the association in a large, community-based sample of women living with HIV could help quantify the relationship.

Our study aimed to explore the relationship between timing of an HIV-positive diagnosis and utilization of PMTCT services among a large, representative sample of mothers living with HIV. We hypothesized that women who were aware of their HIV-positive status prior to pregnancy would complete more services than women learning of their HIV-positive status during ANC of their pregnancy.

Methods

This study utilizes two rounds of serial cross-sectional survey data collected for the impact evaluation of Zimbabwe's national PMTCT program. The two surveys, in 2012 and 2014, measured service utilization levels before and after the implementation of Option A of the 2010 WHO guidelines. Option A provided women not yet qualifying for lifelong antiretroviral therapy (i.e. CD4 count > 350 cells/ml) with azidothymidine (AZT) starting at 14 weeks gestation and postpartum AZT or nevirapine (NVP) prophylaxis for infants depending on their breastfeeding status.¹ The impact evaluation was designed to assess the impact of Option A on mother-to-child HIV transmission and HIV-free survival among 9-18 month old infants; an age range that captures infections occurring during gestation, delivery, and breastfeeding. Zimbabwe has since implemented Option B+ of the 2013 WHO guidelines, which precludes the need for a CD4 test by placing all pregnant women on lifelong ART regardless of stage of disease.¹⁵

Study population

Biological mothers and caregivers aged 16 years and older with infants born 9-18 months prior to the survey date were eligible to participate. Mother/caregiver-infant pairs were not excluded if the infant was no longer alive, as HIV-infected children have a high probability of death in the first two years of life.^{16,17,18} For this analysis, we limited the sample to only biological mothers with a self-reported HIV-positive test result (n=2093). We then excluded mothers who self-reported they were diagnosed HIV positive at delivery (n=49), given that their experience would be slightly different from those mothers diagnosed at early stages. Therefore, our final sample included only those mothers with a self-reported diagnosis prior to pregnancy or during ANC. We further excluded 105 women from the analysis who had missing values for the CD4 test question, 102 of whom were diagnosed prior to pregnancy. The final analytic sample was N=1939. Although most study covariates had no missing values, in instances where there were missing values, none had more than 0.10% missing values.

Sampling

We purposively sampled five provinces (Harare, Manicaland, Mashonaland Central, Mashonaland West, and Mataberland South) to represent the geographic, ethnic, linguistic, and HIV-prevalence diversity of the country. We used multi-staged probability sampling to first select 157 health facilities offering PMTCT services and then eligible mother-infant pairs in the surrounding catchment area. Multiple sources were used to create a list of households with births in the last two years. These sources included infant immunization records, village health workers and village heads living and working in the roughly 10-kilometer radius of the selected health facilities. All households identified as having had a birth within the last two years were assessed for eligibility. Eligible mother-infant pairs were then randomly selected for participation according to the pre-determined sampling fraction for that catchment area. A detailed description of the sampling strategy was published previously.¹⁹

Data Collection

Data collection occurred April-September 2012 for the baseline and July-December 2014 for the follow-up. During both survey rounds, after providing written informed consent, mothers completed an interviewer-administered questionnaire on handheld, personal digital assistants.

The survey included questions on demographic characteristics, HIV testing history, and utilization of key PMTCT services. Given the sensitive nature of the survey, no personal or household-level identifiers were collected during data collection to ensure complete anonymity of all study participants.

Data Analysis

We generated descriptive statistics on the entire study sample, as well as stratified by timing of diagnosis. We used self-reported HIV testing and diagnosis history to categorize participants as being diagnosed either prior to the pregnancy with the eligible infant, or *index pregnancy*, or during ANC of the index pregnancy. We explored utilization of key PMTCT services, specifically the self-reported receipt of a CD4 test, any maternal prophylactic ARVs or ART, any infant prophylactic ARVs, and an infant HIV test. While we asked to view maternal and child health cards to validate diagnosis history and utilization of services, not all women had or were willing to share their cards. Therefore, we relied solely on self-reported responses. Although CD4 testing is no longer indicated for countries implementing Option B+, at the time of the surveys the PMTCT guidelines employed by Zimbabwe required all HIV-positive pregnant women to undergo a CD4 test to determine if they should be placed on prophylactic ARVs for the purposes of PMTCT or on lifelong ART for their own health. Comparisons between prior to pregnancy and ANC diagnoses were conducted using the Rao Scott correction of Pearson's chi-squared statistic due to the complex sampling strategy of the data.^{20,21} Given the importance of women completing all of the services (CD4 test, maternal ARVs/ART, infant ARVs, and infant HIV test), we then created a three-level outcome variable to capture different levels of utilization, categorized as: zero, some (1-3 services), and complete (4 services) service utilization. Although we were most interested in exploring differences in complete utilization by timing of diagnosis, we thought it would also be important to examine partial utilization. We utilized a three-level outcome variable so that the categories had roughly similar sizes. We then used multinomial logistic regression to explore the presence of an association between the timing of diagnosis and these levels of service utilization.

Covariates were selected *a priori* based on evidence of an association with service utilization in previous studies and those that were potential confounders. These included maternal age, parity, pregnancy intention, maternal educational attainment, marital status, number of individuals living in the household, religion, province, a proxy variable for wealth, and survey round.^{9,12,22,23,24} See **Table 1** for variable categories. We used polychoric principal components analysis to generate a proxy for wealth from: household assets, the primary material used in the construction of the household, source of drinking water, and type of toilet facility. This index was then divided into quarters.

All analyses utilized weighted counts to account for the complex sampling structure and the correlated nature of the data within health facility catchment areas. We used STATA 13 (Stata Corporation, College Station, Texas) to conduct all analyses. We assessed models for hypothesized two-way interactions, as well as multicollinearity by assessing variance inflation factors and correlation matrices. Interactions were retained when the p-value was <0.05 on the interaction term.

Human Subjects

The protocol and survey instruments for this study were reviewed and approved by the Medical Research Council of Zimbabwe, and the Institutional Review Boards at the University of California, Berkeley and University College London.

Results

We conducted the analyses on a weighted count of 1938.97 women (based on 1,939 observations); 964.6 (50%) had self-reported HIV-positive diagnosis prior to pregnancy and 974.4 (50%) were diagnosed during ANC. Each survey round accounted for nearly half of the sample size, 48% (2012) and 52% (2014). Average age was 29.6 years (range: 16-59), mean lifetime parity of 3.1 births, and average household size of 5.1 inhabitants. Eighty-four percent were currently married and 32% reported the index pregnancy had been unplanned (**Table 1**). Sociodemographic characteristics were largely similar for the two diagnosis categories. However, women diagnosed prior to the current pregnancy tended to be older and to have higher parity. Ninety-eight percent of mothers reported accessing ANC at a health facility at least once during their pregnancy and 74% attended the WHO-recommended 4 or more visits. Overall, utilization of each service step was high: 62% received a CD4 test, 79% received maternal ARVs, 78% received infant ARVs, and 72% received an infant HIV test. Fifteen percent (n=299) of mothers utilized zero services, 34% (n=654) utilized some services, and 51% (n= 987) utilized all services.

Service utilization by timing of diagnosis

Self-reported utilization of each service (CD4 test, maternal ARVs/ART, infant ARVs, and infant HIV test) increased between 2012 and 2014, particularly among women diagnosed prior to pregnancy. (**Table 2**) In bivariate associations, self-reported utilization of each service was associated with diagnosis timing, with the exception of a CD4 test in 2014. In 2012, 50% of women diagnosed prior to pregnancy received any maternal ARVs compared to 83% of women diagnosed during ANC (p-value <0.001). In 2014, 94% of women diagnosed prior to pregnancy received any maternal ARVs compared to 86% of women diagnosed during ANC (p-value = 0.001). Additionally, in 2012, 46% of women diagnosed prior to pregnancy had their infant tested compared to 67% of women diagnosed during ANC (p-value <0.001). In 2014, 91% of women diagnosed prior to pregnancy and 83% of women diagnosed during ANC (p-value = 0.003) reported their infants were tested for HIV.

We observed dramatic shifts in levels of utilization within each diagnosis category between 2012 and 2014, as well as between the two diagnosis categories (**Figure 1**). In 2012, only 27% and 30% of women diagnosed prior to pregnancy completed all or some of the services, respectively, whereas 40% and 54% of women diagnosed during ANC completed all or some of the services, respectively. The marked heterogeneity between the two groups in 2012 appreciably is absent in 2014. Specifically, there was a sharp decline in zero service utilization among women diagnosed prior to pregnancy, from 43% to 3%. Additionally, in 2014, 67% of

both women diagnosed prior to pregnancy and women diagnosed during ANC received all services.

Given the presence of significant interaction between the timing of diagnosis and survey year (p -value for interaction < 0.001 at both levels of comparison) in the model with all study covariates, we stratified the adjusted multinomial analysis by survey year. (**Table 3**) In 2012, mothers diagnosed during ANC were more likely to utilize some compared to zero services (OR_a 15.02, 95% CI: 7.86, 28.70) and all compared to zero services (OR_a 13.25, 95% CI: 6.30, 27.87), adjusting for maternal age, education level, parity, pregnancy intention, marital status, household size, religion, province, wealth index, and survey year. In 2014, the association reversed. Diagnosis during ANC reduced the odds of utilizing some compared to zero services (OR_a 0.26, 95% CI: 0.11, 0.64) and all compared to zero services (OR_a 0.36, 95% CI: 0.16, 0.79).

Other factors significantly associated with service utilization

In 2012, increased maternal age was associated with higher odds of utilizing all compared to zero services (OR_a 1.12, 95% CI: 1.05-1.19), and reporting that the pregnancy was unplanned was also associated with higher odds of utilizing some compared to zero services (OR_a 3.01, 95% CI: 1.83-4.95) and all compared to zero services (OR_a 2.98, 95% CI: 1.74-5.10). These associations did not remain significant in 2014. In 2012, larger household size was negatively associated with utilization of some compared to zero services (OR_a 0.88, 95% CI: 0.78-0.99) and all compared to zero services (OR_a 0.81, 95% CI: 0.71-0.93). This association did not remain significant in 2014.

Discussion

Our study explored how the timing of an HIV-positive diagnosis relative to a woman's pregnancy, either prior to the index pregnancy or during ANC with the index pregnancy, might be associated with utilization of PMTCT services. Overall, the percent utilization of each of the services examined increased between the 2012 and 2014 surveys. The increased utilization of PMTCT services over the two-year period is consistent with the results observed elsewhere from global efforts to increase access to and utilization of PMTCT services to meet the global goal of reduced transmission rates to below 5% by 2015.¹

We observed important shifts in service utilization between the two diagnosis categories over time. Utilization of each of the services examined was much lower for women diagnosed prior to pregnancy compared to women diagnosed during ANC in 2012. Only two years later, in 2014, that difference had not only disappeared, for all the services except receipt of a CD4 test, the direction had reversed, with higher utilization among previously diagnosed women. Thus, the pattern in 2014 is consistent with our hypothesis and with Technau et al's results in South Africa. They found that women diagnosed prior to pregnancy had their infants tested for HIV earlier than women who learned during or post-pregnancy (7 weeks, 11 week, and 31 weeks, respectively).¹⁴ They also found that women diagnosed prior to pregnancy were more likely to receive maternal ARVs, although significance was only achieved when compared to women who learned of their status post-delivery.

To further explore the relationship between utilization and timing of diagnoses, we conducted a multivariate multinomial logistic regression. We found that, although in 2012 there were markedly different service utilization patterns (zero, some, all) between women diagnosed prior to pregnancy and women diagnosed during ANC, in 2014 those differences between the two groups had all but disappeared. The interaction between the timing of diagnosis and the survey year in the multinomial regression confirms the magnitude of the shift in service utilization among women diagnosed prior to pregnancy between the two survey rounds. Zimbabwe rapidly scaled-up their PMTCT program and the implementation of Option A in all of their clinics offering PMTCT in 2012.²⁵ The greater access to services and any associated increase in the quality of care likely contributed to the increased utilization over time, particularly among women diagnosed prior to pregnancy. For example, a fundamental part of the enhanced program was to increase access to point-of-care CD4 testing machines.²⁶ In our study sample, receipt of a CD4 test increased by 38% among women diagnosed prior to pregnancy and by 17% among women diagnosed during ANC. Further, perceived stigma associated with having conceived while knowingly HIV-positive could have inhibited women diagnosed prior to pregnancy from seeking PMTCT services in 2012, and contributed to the high percentage of these women utilizing zero services.^{27,28,29,30} With greater availability of more efficacious drug regimens for PMTCT overtime, those negative pressures may have decreased and resulted in greater uptake of services in subsequent years.

Another potential explanation for the dramatic shift in the service utilization pattern among women diagnosed prior to pregnancy could be that as the PMTCT program evolved and women gained experience utilizing PMTCT services in previous pregnancies their utilization of additional services in subsequent pregnancies also increased.^{9,11} If these women had experience utilizing PMTCT service in earlier pregnancies where transmission to the infant did not occur they might have been more convinced of the effectiveness of the program, and therefore, decided to utilize additional services in subsequent pregnancies. Unfortunately, the survey did not collect data on prior utilization of PMTCT services or on the infection status of prior children.

Among women diagnosed during ANC, the share with zero utilization is very small, and increased slightly (from 6% to 10%) by 2014. This is contrary to what we would expect. The increase could partially be due to the increase in length of treatment adherence required under Option A. Although this study did not examine adherence to the drug regimens prescribed to mothers, it is possible the longer period of adherence required under Option A overwhelmed those mothers who had just learned of their HIV-positive status during the same clinical interaction causing them not to complete other services. A similar pattern of utilization and timing of diagnosis was observed in Malawi, where pregnant women initiated on lifelong ART on the same day as their diagnosis were twice as likely not to return to the clinic.³¹ Alternatively, the increase among women diagnosed during ANC who utilized zero services could simply be a result of the program increasing the number of women who attend ANC and learned their HIV-status, but who normally are resistant to utilizing service in health facilities and therefore, were reluctant to utilize any of the other PMTCT services. Finally, the difference

might also reflect changes in the composition of the population being diagnosed during pregnancy. They may be more likely to be younger and primiparous than that same population was in 2012 as a higher proportion of women receive services.

Limitations of this study include the use of self-reported timing of diagnosis and service utilization. Although dried blood spot samples were collected as part of the impact evaluation, we were unable to verify timing of diagnosis against medical records and therefore, depended on the self-reported testing and diagnosis history. Although we asked participants if we could view their maternal and child health cards to verify their service utilization, not all mothers had these cards available or were willing to share these cards with the survey interviewer. Additionally, analyses only included those services administered at a health facility, and did not examine adherence to drug regimens or other personal behaviors like breastfeeding practices, which are equally critical to preventing pediatric infections. Further, given that overall service utilization increased between 2012 and 2014, there were fewer women who completed zero services in 2014, reducing the size of the comparison population. Therefore, it is possible that reduced power of the comparison between some or all service utilization and zero service utilization might be a partial factor in the differences in association found in 2012 and 2014.

The significant increase in service utilization between 2012 and 2014 highlights how rapidly and effectively Zimbabwe was able to roll out Option A of the 2010 WHO treatment guidelines and improve uptake of PMTCT services.¹ The dramatic increase in service utilization among women diagnosed prior to pregnancy is especially remarkable. As the country transitions to Option B+, requiring lifelong ART adherence and engagement with the health system, it will be important to examine additional methods for supporting women at various stages of learning their HIV-positive status to ensure consistent, high-level PMTCT service utilization. Differences in PMTCT service utilization between mothers diagnosed prior to pregnancy and women diagnosed during ANC present an additional layer of complexity to PMTCT programs. Other countries should consider exploring differences in PMTCT service utilization by timing of diagnosis. Countries that have not yet achieved the reversal that Zimbabwe has may be motivated to emulate the Zimbabwean success and for outcomes overall to improve over the longer-term.

Table 1: Demographic characteristics of HIV+ women with 9-18 month year olds in Zimbabwe stratified by timing of diagnosis

Characteristic	Total		HIV+ Prior to Pregnancy		HIV+ During ANC		P-value
	N	(%)	N	(%)	N	(%)	
Total	1939.0	100.0	964.6	49.8	974.4	50.3	
Education							0.381
Primary or less	612.1	31.6	301.9	31.3	310.2	31.8	
Forms 1-3	592.4	30.6	275.4	28.6	317.0	32.5	
Form 4	686.4	35.4	360.7	37.4	325.7	33.4	
Form 5+	48.0	2.5	26.6	2.8	21.4	2.2	
Marital Status							0.095
Not Married	304.5	15.7	135.5	14.1	169.0	17.4	
Currently Married	1632.0	84.3	827.0	85.9	805.3	82.7	
Pregnancy Intention							0.215
Desired	1047.0	54.0	504.9	52.3	542.4	55.7	
Mistimed	265.1	13.7	127.8	13.3	137.3	14.1	
Unplanned	626.6	32.3	331.9	34.4	294.7	30.2	
Province							0.002
Harare	478.8	24.7	259.3	26.9	219.5	22.5	
Manicaland	582.1	30.0	324.0	33.6	258.1	26.5	
Mashonaland Central	292.7	15.1	133.6	13.9	159.1	16.3	
Mashonaland West	294.0	15.2	113.6	11.8	180.4	18.5	
Matabeleland South	291.4	15.0	134.1	13.9	157.3	16.1	
Religion							0.892
Roman Catholic	119.0	6.1	63.5	6.6	55.5	5.7	
Apostolic	620.4	32.0	299.8	31.2	320.6	32.9	
Pentacostal	415.4	21.5	207.9	21.6	207.5	21.3	
Other	539.1	27.8	268.6	27.9	270.6	27.8	
No religion	242.9	12.5	122.8	12.8	120.1	12.3	
Wealth Index (quarters)							0.685
1	419.9	21.7	208.1	21.6	211.8	21.7	
2	365.9	18.9	188.6	19.6	177.4	18.2	
3	461.0	23.8	226.9	23.6	234.1	24.0	
4	690.0	35.6	339.0	35.2	351.0	36.0	
Survey Year							0.310
2012	933.1	48.1	476.4	49.4	456.6	46.9	
2014	1006	51.9	488.2	50.6	517.7	53.1	
Age, years (Mean, SE)	29.6	0.2	30.3	0.2	28.9	0.3	< 0.001
Household Size (Mean, SE)	5.1	0.1	5.2	0.1	5.0	0.1	0.095
Parity (Mean, SE)	3.1	0.1	3.2	0.1	2.9	0.1	< 0.001

Table 2: Comparative service utilization by diagnosis timing and survey years (N=1939)

Service	Total (%)	Diagnosis Timing		P-value
		HIV+ Prior to Pregnancy (N=965) (%)	HIV+ during ANC (N=974) (%)	
CD4 test				
2012	47.3	36.8	58.3	0.001
2014	75.1	74.6	75.5	0.740
Maternal ARVs*				
2012	66.5	50.5	83.2	< 0.001
2014	90.0	94.4	85.8	0.001
Infant ARVs⁺				
2012	64.5	47.5	82.2	< 0.001
2014	90.4	94.6	86.5	0.01
Infant HIV test				
2012	56.0	45.7	66.7	< 0.001
2014	86.9	90.7	83.2	0.003
Zero services utilized				
2012	24.96	43.4	5.7	< 0.001
2014	6.55	3.0	9.9	0.001

* Antiretroviral prophylaxis (ARV) or combination antiretroviral therapy (ART)

⁺ Antiretroviral prophylaxis (ARV)

Figure 1: Service utilization levels (zero, some, all) by diagnosis timing and survey year

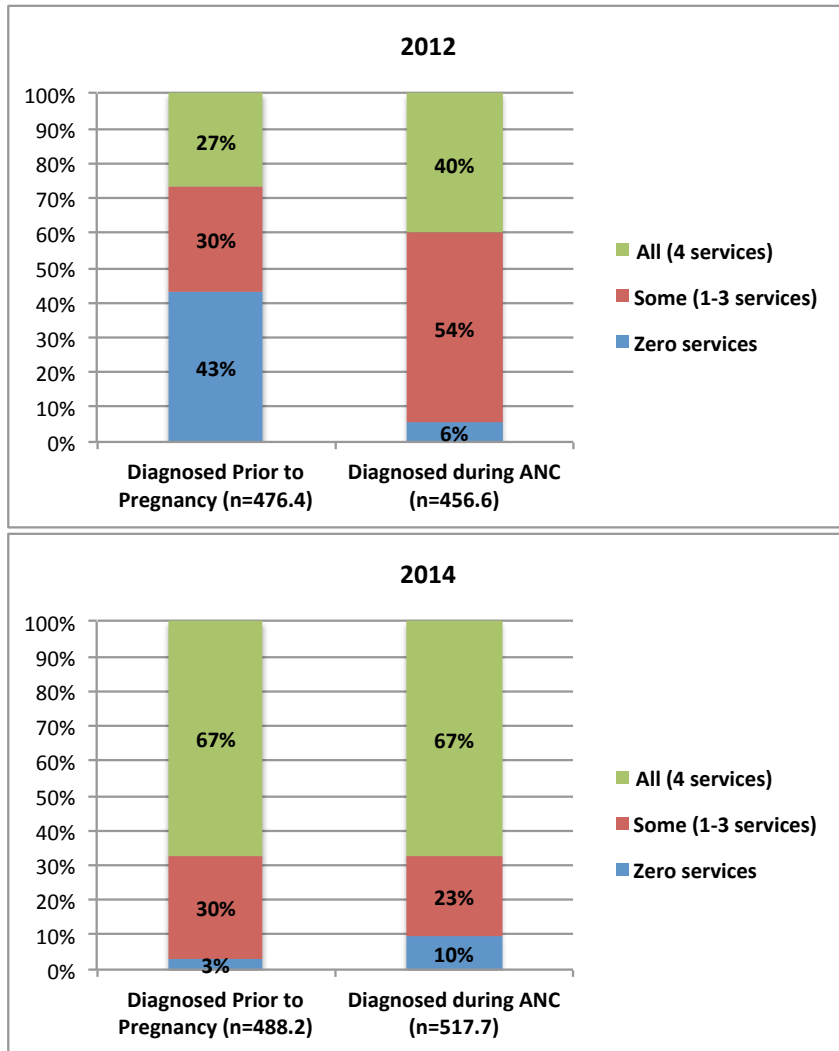


Table 3: Adjusted multinomial analysis stratified by survey year

	2012 Survey (N=929)		2014 Survey (N=1006)	
	Model P-value <0.001		Model P-value <0.001	
	Some vs Zero OR [95% CI]	All vs Zero OR [95% CI]	Some vs Zero OR [95% CI]	All vs Zero OR [95% CI]
ANC Diagnosis	15.02*** [7.86,28.70]	13.25*** [6.30,27.87]	0.26** [0.11,0.64]	0.36* [0.16,0.79]
Maternal Age	1.04 [0.99,1.10]	1.12*** [1.05,1.19]	1.06 [0.96,1.17]	1.06 [0.97,1.15]
Form 1-3 Education	0.78 [0.42,1.47]	0.92 [0.47,1.81]	0.61 [0.25,1.51]	0.93 [0.39,2.20]
Form 4 Education	0.47* [0.24,0.91]	0.6 [0.31,1.17]	0.37** [0.18,0.76]	0.73 [0.35,1.54]
Form 5+ Education	1.08 [0.12,9.79]	0.62 [0.10,3.71]	0.17 [0.03,1.15]	0.22 [0.03,1.41]
Parity	1.15 [0.84,1.57]	0.98 [0.73,1.31]	0.93 [0.70,1.23]	1.1 [0.83,1.45]
Mistimed pregnancy	0.88 [0.44,1.77]	0.88 [0.44,1.75]	0.56 [0.19,1.61]	0.7 [0.34,1.42]
Unplanned pregnancy	3.01*** [1.83,4.95]	2.98*** [1.74,5.10]	1.2 [0.63,2.26]	1.12 [0.57,2.22]
Currently married	0.51 [0.26,1.01]	0.51 [0.26,1.00]	0.57 [0.22,1.50]	0.74 [0.30,1.85]
Household Size	0.88* [0.78,0.99]	0.81** [0.71,0.93]	0.98 [0.83,1.16]	0.92 [0.79,1.07]
Manicaland Province	1.59 [0.76,3.30]	1.79 [0.72,4.47]	2.67* [1.18,6.08]	2.79 [0.96,8.08]
Mashonaland Central Province	1.28 [0.68,2.40]	0.94 [0.41,2.20]	3.08* [1.11,8.51]	5.53** [1.56,19.54]
Mashonaland West Province	5.01** [1.80,13.97]	3.01 [0.96,9.48]	3.69** [1.54,8.83]	5.01** [1.80,13.91]
Matabeleland South Province	7.22*** [2.37,21.97]	5.29*** [2.00,14.02]	3.34 [0.77,14.47]	5.90* [1.22,28.56]
Apostolic Religion	0.64 [0.20,2.05]	0.8 [0.29,2.18]	0.42 [0.16,1.09]	0.51 [0.19,1.39]
Pentacostal Religion	0.46 [0.14,1.49]	0.56 [0.19,1.66]	0.89 [0.20,3.87]	1.27 [0.45,3.65]
Other Religion	0.44 [0.12,1.71]	0.57 [0.19,1.68]	1.03 [0.35,3.01]	0.98 [0.31,3.06]
No Religion	0.32	0.27*	0.95	0.91

	[0.08,1.31]	[0.08,0.96]	[0.22,4.06]	[0.22,3.76]
Wealth Index 2	1.42	1.48	1.02	0.98
	[0.70,2.86]	[0.60,3.66]	[0.43,2.42]	[0.41,2.33]
Wealth Index 3	1.32	1.72	1.06	1.03
	[0.67,2.60]	[0.84,3.54]	[0.47,2.38]	[0.47,2.25]
Wealth Index 4	0.97	1.79	2.48	2.87
	[0.42,2.23]	[0.79,4.02]	[0.79,7.77]	[0.92,8.89]

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

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Paper 3: Option B+ implementation strategies to improve antiretroviral treatment adherence in Malawi: a policy analysis

Abstract

The mother-to-child HIV transmission rate in Malawi has decreased significantly since the adoption of Option B+, a treatment regimen that places all pregnant or breastfeeding women living with HIV on lifelong antiretroviral therapy (ART) regardless of their stage of disease or CD4 count. However, lifelong adherence to ART remains challenging. We proposed two implementation strategies to improve adherence: 1) for all pregnant/breastfeeding women to initiate and indefinitely receive treatment at maternal and child health (MCH) clinics rather than be transferred to an ART specialty clinic, and 2) to offer the option to initiate lifelong ART, regardless of stage of disease, to any individual living with HIV in the pregnant/breastfeeding woman's household. We evaluated each strategy on whether it has the potential to: significantly increase adherence among women initiating treatment for PMTCT, maintain or improve equitable access to antiretroviral therapy, increase health benefit from available resources, and be feasible within Malawi's evolving healthcare infrastructure. We concluded that both strategies could be effective at increasing ART adherence and feasible within the current healthcare infrastructure within Malawi.

Introduction

Adherence to antiretroviral therapy (ART) for the prevention of mother-to-child HIV transmission (PMTCT) remains below optimal levels in Malawi. Low adherence to PMTCT drugs is a historical problem. However, with the recent implementation of Option B+, a protocol that requires the initiation of pregnant and breastfeeding women on lifelong ART, sustaining high levels of ART adherence is even more important. Adherence is required for ART to effectively reduce mother-to-child transmission rates, as well as to protect the health of the mother.

Malawi has made significant progress in initiating pregnant/breastfeeding women on ART since implementing Option B+ in 2010. It has reduced mother-to-child transmission rates by 67% between 2009 and 2013.¹ However, early findings show that attrition at six and twelve months post-initiation are 17% and 23%, respectively.² Although attrition may appear fairly low, ART is only effective at reducing transmission rates when consistently ingested. Additionally, the breastfeeding period in Malawi typically lasts for 24 months. Mothers who are non-adherent while their infants are still exposed to HIV through breast milk are at greater risk for transmitting HIV. Therefore, better strategies to improve long-term adherence are needed for the viability and success of Malawi's PMTCT program.

Having pioneered the transition to Option B+, Malawi now has the opportunity to further lead the way in adopting strategies that could improve adherence levels. This paper examines two strategies that Malawi could implement to improve ART adherence levels among women initiating ART during pregnancy/breastfeeding. The viability of the two strategies, however,

depends on whether they interfere with the equitable distribution of ART, whether they maximize health benefit with available resources, and the degree to which their implementation is feasible.

Background

Although mother-to-child HIV transmission rates are declining, there were an estimated 240,000 children newly infected with HIV globally in 2013.¹ Antiretroviral drugs are the main driver for the lowering transmission rates, and their usage has evolved dramatically over the past decade. Where once adherence required only the ingestion of a single dose of a drug at the onset of labor, PMTCT programs globally now require adherence to drug regimens throughout pregnancy and breastfeeding, if not indefinitely.^{3,4,5,6} The current recommendation set forth by the World Health Organization is to place all pregnant women living with HIV on lifelong, combination antiretroviral therapy (ART). This recommendation, called Option B+, has the potential to reduce mother-to-child HIV transmission rates from 25-35%, in absence of intervention, to below 5%, while also reducing previously identified barriers to treatment.^{5,6} However, poor adherence and loss to follow-up from PMTCT programs are important problems that reduce program effectiveness and can be costly to the health system and to the woman's own health.

History of Option B+

In 2010, the World Health Organization (WHO) released PMTCT treatment guidelines that introduced two treatment regimens.⁵ Ministries of Health determined which of the two options to implement within their PMTCT program. Under both options, women living with HIV with a CD4 test* result of ≤ 350 cells/ml, the treatment eligibility threshold at the time, were placed on lifelong, combination antiretroviral therapy. For all other women living with HIV, i.e. those who would not be eligible for treatment if they were not pregnant, countries implemented one of two options:

- Option A, which placed women on azidothymidine (AZT) starting at 14 weeks gestation followed by infant doses of nevirapine during the breastfeeding period, or
- Option B, which placed women on ART throughout pregnancy and breastfeeding.

When considering which of the above regimens to implement, the country of Malawi decided to modify Option B to better fit their epidemic context and the constraints of their health system, which they coined 'Option B+'.⁷ Given the limited availability of CD4 testing within their health system and the high fertility rate among their population, Malawi decided to place all pregnant women living with HIV on lifelong ART regardless of stage of disease or CD4 count. This decision eliminated the need for CD4 testing to initiate treatment for pregnant women, as well as the start and stop of treatment between pregnancies. By continuing treatment between pregnancies, the mother's viral load would be lower prior to the conception of her subsequent

* A CD4 test is used to determine how advanced an individual's HIV-infection has progressed. The lower the CD4-cell count, the more progressed the stage of disease.

children, further minimizing the risk of transmission to both her sexual partner(s) and her subsequent children.^{7,8} Between July 2011 and September 2012, after one year of Option B+ implementation, Malawi increased the number of women started on ART by 748%.²

Based on early findings from Malawi and growing interest from the international community, the WHO further revised their PMTCT treatment guidelines in 2013 to include Option B+ on the recommended treatment list, while also removing Option A as a recommended strategy.⁶ The 2013 guidelines also increased the recommended treatment eligibility threshold for all individuals living with HIV from CD4 count ≤ 350 to ≤ 500 cells/ml. While some countries continued to implement Option B, the changes to the WHO recommendations led several high HIV-prevalence countries to follow Malawi's lead and adopt Option B+ into their national PMTCT programs. As of February 2015, 18 of the 22 countries with the highest burden of HIV among pregnant women have started to switch their national program to include Option B+.⁹

There are a number of reasons why PMTCT stakeholders and researchers believe Option B+ will have a more significant impact on the HIV-epidemic than other PMTCT regimens.

- When a patient adheres to ART, his/her viral load is lowered, and therefore, his/her infectiousness is reduced.^{10,11} Thus, ART is highly effective for not only reducing transmission to the infant, but also to the woman's uninfected sexual partners.⁸
- ART is the most effective treatment available for improving the health of individuals living with HIV. By keeping mothers healthy, and reducing the likelihood of developing co-infections, maternal survival improves.^{6,12} Improved maternal health also increases an infant's likelihood of survival.^{13,14}
- Treatment is standardized so that all pregnant women initiate the same drug regimen.¹⁵ This standardization eliminates the need for CD4 testing to determine if a woman should be placed on PMTCT prophylaxis or on lifelong treatment. This is expected to decrease the number of woman who do not receive timely treatment because they did not complete the CD4-test step. Standardization also eases the burden on health facilities, as they only have to train their staff to administer and to stock one drug regimen.
- Women will not have to start and stop treatment between pregnancies or between pregnancy and meeting the treatment threshold which may reduce the development of drug resistance associated with starting and stopping treatment.¹⁶
- It is difficult to convincingly explain to people on ART that it is extremely important for them to never interrupt their ART treatment because it fosters resistance if the national program regularly starts and stops people's treatment. Thus, Option B+ should strengthen adherence to ART.
- Option B+ is cost-effective compared to the other treatment options available if one considers the benefit of reduced HIV transmission, the relatively high cost of monitoring women to detect when they become eligible for treatment, the cost of ART resistance caused by starting/stopping treatment and the reduced effectiveness associated with women being lost-to-follow-up while they are waiting to become eligible.^{17,18,19} It strategically capitalizes on enrolling women already utilizing health services rather than

having to seek and re-engage these same women at some point in the future to enroll them in treatment when they become eligible.

Despite the significant potential Option B+ could have on reducing pediatric HIV infections and improving maternal and population health, issues with long-term adherence remain a major concern. Poor adherence to antiretroviral drugs for PMTCT and loss-to-follow up is not a new problem. Even when PMTCT interventions involved single dose regimens ingested by the mother at the onset of labor and by the infant following delivery, one study found only 51% of mother-infant pairs were adherent.²⁰ In Malawi, following the implementation of Option B+, loss-to-follow-up at six and twelve months was found to be 17% and 23%.^{2,21} Additionally, a systematic review of ART adherence of 51 studies from high-, middle-, and low-income countries during and after pregnancy found that adherence levels decrease following delivery. In that study, the pooled estimate showed only 53% of women had adequate adherence post-partum compared to 76% adequate adherence during pregnancy.²² Adherence throughout pregnancy and the entire breastfeeding period are essential to achieve lower transmission rates.

When treatment regimens are not followed as instructed, viral loads are not sufficiently suppressed, and the effectiveness of the drug regimens to reduce mother-to-child HIV transmission rates declines. Additionally, non-adherence increases the potential development of drug resistance. If individuals develop drug resistance to first-line drug regimens they will have to be placed on second and third-line drug regimens, which are much more expensive and limited in availability.²³ The development of drug-resistance also facilitates the transmission of drug-resistant strains of the virus on to others.²⁴ Some evidence has suggested that initiation of ART by pregnant women who are not yet HIV symptomatic can be associated with reduced adherence.²¹ If their adherence is sufficiently low, then the reduced effectiveness coupled with the increased rate of development of resistance could more than outweigh the benefits of early initiation.

Malawian Context

Malawi is a small, landlocked country in Sub-Saharan Africa with a population of 16.7 million.²⁵ It is approximately the same size as Pennsylvania with one third of its population. Malawi's population has doubled since 1987.²⁶ A major contributor to population growth is the high total fertility rate of 5.7 births.²⁷ Each year there are an estimated 608,000 births,²⁸ and 95% of pregnant women attend at least 1 antenatal care (ANC) visit during their pregnancy.²⁷ However, only 46% attend the WHO recommended 4 visits.²⁷ Average household size is 4.6 people.²⁷

Malawi has one of the highest burdens of HIV prevalence globally. The last national estimates indicate an adult (age 15-49) prevalence of 10.6%, with higher prevalence among women (12.9% among women vs. 8.1% among men).²⁷ Incidence, however, is declining. Since 2010, the number of new HIV infections decreased by 41%.¹ Most new infections (67%) in Malawi are estimated to occur among people in married or cohabitating heterosexual partnerships.²⁹

Therefore, strategies to decrease transmission among sero-discordant couples[†], through increased condom use, scale-up of ART and circumcision of uninfected male partners, are important steps to further decreasing incident HIV-infections. The use of antiretroviral drugs by the uninfected partner (PREP, or pre-exposure prophylaxis) has also been studied but it is a strategy that makes economic sense only when it is not possible to achieve ART adherence and viral suppression[‡] in the infected partner.^{30,31} Longer-term prevention strategies aim to also reduce the number of sero-discordant partnerships by improving primary prevention and encouraging sero-sorting, or the formation of new partnerships between people of like infection status.

In addition to strengthening its prevention efforts, Malawi continues to make significant progress towards providing treatment to the estimated 1.1 million individuals living with HIV.³² Since the inception of Malawi's ART program in 2004, the scale-up of ART has resulted in an estimated gain of 1.4 million life-years and 275,000 deaths averted.²⁹ As of December 2014, 533,027 individuals were receiving treatment.²⁹

Treatment eligibility in Malawi follows the 2013 WHO treatment guidelines,^{6,33} which indicate that the following individuals living with HIV are eligible to receive ART:

- Individuals with a CD4 count ≤ 500 cells/ml
- All pregnant and breastfeeding women
- All children under 5 years of age
- Individuals in sero-discordant partnerships

The WHO guidelines also state that individuals with CD4 < 350 cells/ml or very advanced HIV-disease should be prioritized.

In 2013, 83% of individuals eligible for ART in Malawi received it. This figure dropped in 2014 to 67% following the increased WHO treatment threshold to CD4 ≤ 500 cells/ml, which increased the denominator for eligibility.²⁹ However, Malawi continues to initiate over 100,000 individuals on ART each year,²⁹ a figure which they hope will increase. Malawi estimated that there were 798,000 individuals eligible for treatment in 2014.²⁹ This suggests that roughly 72% of all individuals living with HIV in Malawi already qualify for treatment.

[†] A couple in which one person is HIV-infected and the other is not. They are referred to as "sero"-discordant, reflecting the fact that anti-HIV antibodies can be found in the serum of one of the partners but not the other. Since the correlation between sero-status and infection status for HIV is virtually 100%, sero-discordance is equivalent to infection-discordance.

[‡] Antiretroviral drugs interfere with the replication of the HIV virus. Thus, if treatment is effective, the HIV virus is not replicating and not being released in significant numbers from cells. This is referred to as "viral suppression". When treatment is maximally effective, currently available tests that quantify viral particles in blood (viral load tests) do not detect any viral particles. Such individuals are said to have "undetectable" virus, a hallmark of effective viral suppression.

Resources

There are 1060 health facilities in Malawi, 78% of which (825) offer HIV testing. Availability of HIV-testing is highest at hospitals and health centers (95% at each), but less likely to be available at dispensaries or other smaller health posts.³⁴ Additionally, 706 facilities currently dispense ART, an increase from 300 facilities in 2011.²⁹ Of the government-operated facilities with PMTCT services, 97% had ART available on the day of site visits undertaken as part of the Service Provision Assessment 2013-2014.³⁴ The high level of ART availability is the result of Malawi's parallel ART supply system, which is distinct from distribution mechanisms of other health supplies. Malawi developed this system in an effort to reduce shortages and stockouts, centralize national purchasing, and increase accountability. Each site is visited every three months to assess supply and need. All ARTs are purchased centrally and distributed back to the sites every three months.³⁵

International donors fund roughly 84% of Malawi's HIV/AIDS response, and 100% of all ART costs.²⁹ Between 2011-2016, Malawi anticipated a cost of US\$563.87 million to scale up access to ART to reach 496,000 adults and children on ART. This figure represented 43% of the overall budget for HIV prevention and treatment.²⁶ An additional US\$53 million were anticipated to scale up high-quality PMTCT services over the same period.²⁶ Importantly, these costs include much more than commodities like ART, but also include the clinic and personnel costs, including training, needed to implement and scale-up the programs. By the end of 2014, Malawi surpassed their goal and had 533,027 individuals on treatment.²⁹

Malawi is at the forefront of PMTCT implementation. Understanding the realities of their healthcare system and identifying barriers that were limiting the effectiveness of their programming, Malawi modified previous WHO recommendations to create Option B+. They pioneered its implementation and have seen reductions in mother-to-child transmission rates, which have decreased by 67% since 2009.¹

The hallmark of Malawi's Option B+ PMTCT program is the decentralization of ART to all health facilities offering PMTCT and maternal and child health services (MCH).² To implement Option B+, Malawi doubled the number of facilities offering ART and implemented policies to allow other health professionals to initiate ART rather than relying solely on physicians.^{7,2} This shift allowed nurses, medical assistants, and midwives who have been certified in PMTCT or ART provision to prescribe and dispense ART.³³ Beyond the decentralization of treatment, however, there was no set mandate on how clinics should manage the continuation of ART care for women initiated on treatment during pregnancy. Therefore, some clinics manage ART care for pregnant women only through pregnancy and breastfeeding, followed by a transfer to an ART specialty clinic, while others initiate the first supply of ART in the MCH clinic and then transfer the woman immediately to an ART specialty clinic for further care.³⁶ Beyond initiation of pregnant/breastfeeding women on ART, Malawi must also identify and implement strategies to improve long-term adherence throughout the duration of the infants' exposure (up to 24 months) and beyond.

The levels of attrition among women initiating ART during pregnancy and breastfeeding⁵ are comparable over the first year to rates among all adults on ART in Malawi, with the twelve-month retention rate reported at 77%.²⁹ However, by sixty months, retention of all adults in ART programs declines to 59%.²⁹ If retention rates among women initiating ART during pregnancy/breastfeeding follow similar patterns as the general population, the potential advantages of Option B+ described above will not be realized.

Malawi committed to striving towards the new UNAIDS 90-90-90 targets, which state that, by 2020, 90% of people living with HIV will be aware of their status, 90% of people diagnosed with HIV will be on ART, and 90% of all people on ART will have viral suppression.³⁷ With even greater levels of individuals being placed on treatment, it is even more essential that adherence levels improve. Although improving adherence levels for all adults is important, the strategies presented here focus only on improving ART adherence among women initiating ART for PMTCT.

Potential Policy Alternatives

We propose two non-mutually exclusive implementation strategies to improve long-term adherence among women initiating ART during pregnancy/breastfeeding in Malawi. Both strategies have varying levels of complexity and potential to improve adherence levels. The two proposed implementation strategies are: 1) for all pregnant/breastfeeding women to initiate and indefinitely receive treatment at maternal and child health (MCH) clinics rather than be transferred to an ART specialty clinic, and 2) to offer the option to initiate lifelong ART, regardless of stage of disease, to any individual living with HIV in the pregnant/breastfeeding woman's household.

Evaluative Criteria

To evaluate the viability of each of the proposed strategies, we assessed whether each option had the potential to:

- significantly increase adherence among women initiating treatment for PMTCT,
- maintain or improve equitable access to antiretroviral therapy,
- increase health benefit from available resources, and
- be feasible within Malawi's evolving healthcare infrastructure.

Projecting the Outcomes

Strategy 1: Provide lifelong ART to women within MCH clinics

While initiation of ART at MCH clinics already exists within their program, complete integration would standardize implementation such that all MCH clinics would continue to dispense first-line ART to women for the duration of their life. Importantly, this strategy would not extend

⁵ As described above, available data show that attrition at six and twelve months post Option B+ initiation are 17% and 23%, respectively, in Malawi.²

beyond providing first-line ART drugs. Stocking second or third-line ART drug regimens, which are used much less frequently, at all MCH clinics would be too costly and beyond the scope of the training of MCH staff. Only 1% of the individuals on treatment in Malawi are currently on second-line ART, so the vast majority of women could still receive their ongoing treatment at MCH clinics.²⁹ Any individuals showing signs of resistance to first-line drugs would be referred to an ART specialty clinic to be evaluated for enhanced adherence support and need for modification of their ART regimen.

Additionally, viral load monitoring, which is required in Malawi at 6 months post-ART initiation and then every 2 years,³³ would not be integrated into MCH clinics. Viral load monitoring, therefore, would continue to be conducted only at specialty clinics. Integration of viral load testing within MCH clinics would require a significant increase in the number of viral load machines and lab personnel capable of performing and interpreting the results. Given that the tests are required infrequently, it would be inefficient for MCH clinics to take on the burden of this task.

Effectiveness

This strategy could improve program effectiveness by reducing the loss-to-follow-up that occurs when individuals are transferred to ART clinics.³⁶ Integration of services is believed to improve service utilization and adherence, and is increasingly promoted by international entities.^{6,38,39} For example, Killam *et al* found that when ART was integrated into ANC clinics, twice as many women eligible for ART initiated treatment prior to delivery than when they were referred to an ART clinic.⁴⁰

This proposal would allow individuals to access HIV services at a location that is not only more convenient, given the greater prevalence of MCH clinics than ART specialty clinics, but that is also not uniquely associated with individuals seeking HIV care and treatment. Therefore, integration can reduce the stigma or potential for inadvertent disclosure associated with accessing services at a specialized ART clinic.^{41,42} Additionally, integration reduces the burden of having to travel to multiple clinics to seek care. In focus group discussions conducted to assess the early implementation of Option B+ in Malawi, women indicated their preference for integrated services. Integration was a timesaver, as they did not have to travel from clinic to clinic to get the different services they or their child might need.³⁵ Although women would still have to go to ART specialty clinics every two years for viral load monitoring, the duration between visits should not deter women from continuing to access the rest of their treatment visits within MCH facilities.

Continued provision of ART services within MCH clinics would ensure continued contact with mother-infant pairs. In Malawi, the median time between births is 36 months.²⁷ Therefore, with average length of breastfeeding lasting 24 months, followed by quick conception of a subsequent child, integration is one way to keep mother-infant pairs in the MCH system. ART appointments are scheduled at intervals of 4, 8, or 12 weeks, with longer appointment gaps given to individuals with demonstrated levels of high adherence.³³ Such regular contact could

not only improve PMTCT related outcomes, but also increase utilization of other health services.

For example, follow-up of HIV-exposed infants remains inadequate. Only 37% of HIV-exposed infants received an HIV test 2 months after delivery.²⁹ Additionally, while 67-70% of HIV-exposed infants are retained in care at 12 months, only 12-14% are retained at 24 months.²⁹ A mechanism to improve the retention of mother-infant pairs at least through the end of the breastfeeding period to determine the final HIV status of the infant is critically important to improving outcomes for HIV-exposed infants. Early infant diagnosis is vital to ensuring HIV-infected infants are on treatment as soon as possible to increase their chances of survival. Therefore, if nurses administering ART review a woman's health card at each visit, they should also remind women of any follow-up visits needed for their infant as well. Through the continued contact with MCH clinics women may also access ANC services earlier in their subsequent pregnancies and more regularly, as well as bringing their children in for routine health visits and immunizations.

Equity

This strategy does not have any positive or negative influence on treatment equity beyond the current treatment guidelines.

Maximize Health Benefit from Available Resources

As this strategy does not increase the number of individuals on treatment, and instead transfers existing drug supplies from ART specialty clinics to MCH clinics, the ART budget should grow in proportion to the success of the strategy. However, additional resource will be needed to ensure that a sufficient number of MCH clinic nurses and medical assistants are continually trained on ART provision and adherence monitoring. Malawi has already scaled up the number of nurses and medical assistants capable of administering ART at MCH clinics, previously training over 4800 individuals, and have mentors in place to provide follow-up training at clinics. However, with the likely increase in the hours of operation devoted to providing ART or the need to employ additional staff to handle increased patient loads at MCH clinics, additional training would ensure that more clinic staff would be able administer and appropriately monitor ART adherence. Monitoring of the performance of MCH clinics would also have to expand to include a greater focus on performance of ART in MCH clinics. Such monitoring should already be in place to monitor the effectiveness of ART during pregnancy, but the system needs to be strengthened, especially if an even larger number of clinics are administering lifelong ART.

Feasibility

The complete integration of ART into MCH clinics would simply expand the existing levels of integration beyond the pregnancy, post-partum, and breastfeeding periods to provide lifelong treatment at MCH clinics. Such an expansion might seem infeasible given that this would add another core service to the mission of MCH clinics. However, it is important to remember that the total fertility rate in Malawi is 5.7, with an average breastfeeding period of 24 months and a median of 36 months between births. Therefore, much of the time women will be accessing

ART treatment will be directly related to PMTCT. ART initiation is available presently at clinics offering ANC, maternity, post-natal and under-5 services, in addition to ART specialty clinics.³³ Currently, there are 619 facilities offering PMTCT services for an estimated 51,484 pregnant women living with HIV in Malawi each year.²⁹ Complete integration of ART into MCH clinics would standardize the level of integration and the duration of time MCH clinics administer ART. This standardization would also help to simplify messaging on how and where to access treatment for women initiating Option B+. Therefore, because integration is recommended in the new treatment guidelines, and some form of integration is already common within Malawi's PMTCT program, this strategy should face minimal political resistance. Additionally, with a greater number of women continuing their care at MCH clinics, wait times at ART specialty clinics should decline, allowing those clinics to better serve the individuals continuing to seek treatment there.

Nonetheless, one major impediment to complete integration of ART into MCH clinics is the question of whether health system capabilities would be able to meet increased demand, and ensure adequate care and patient follow-up.^{43,44,45} However, early evidence from countries implementing Option B+ with some level of integration demonstrates that these barriers are not insurmountable. For example, through the expansion of Option B+, Malawi trained a large number of nurses and other medical assistants on ART guidelines and administration through a train the trainer program. Specifically, Malawi first trained 120 trainers who in turn trained over 4800 health workers, and now has 390 clinical mentors to reinforce the training at the different facilities.³⁵ The existence of a workforce already capable of providing ART services within MCH clinics is a strong indication of the viability of this option. Additionally, the fact that 97% of facilities offering PMTCT services had ART drugs on site at the time of a national survey is an indication that these facilities already have some capability of receiving and storing ART drugs supplies. While adherence levels could be improved, Malawi has retained 77% of women initiated on Option B+ at 12-months. This is also a testament to the feasibility of some level of integration of ART into MCH clinics.

While each MCH clinic currently has health workers capable of ART administration, additional nurses and health assistants will need to be trained to cover the increased demand at MCH clinics. Alternatively, depending on the size of the clinic and the number of patients requiring access to ART services in a given week, dedicated ART providers could simply be transferred from existing ART specialty clinics to the MCH clinics. The transfer of health staff is most viable in larger hospitals and health centers where multiple clinics are located in the same area, so that staff will not be forced to relocate. Further, the transfer of ART clinic staff to MCH clinics would only be feasible if there is currently more than one nurse at ART specialty clinics. Such transfer of ART staff to MCH clinics would require a careful examination of current staffing capabilities and distributions before any changes could be made.

Physical infrastructure of the clinics is another potential barrier to the complete integration of ART into MCH clinics. Malawi is currently undergoing an health infrastructure needs assessment to determine how MCH clinics can be upgraded to better handle patients that require greater levels of privacy and confidentiality, especially patients accessing HIV related services.³⁵ Any

updates would likely improve the feasibility of this strategy. However, in the meantime, some of the smaller clinics might have limited storage capacity for increased ART supplies. For example, Malawi previously distributed drugs to facilities every six months. In an effort to reduce the storage burden on facilities they shortened the distribution window to three months.³⁵ Under this strategy, an additional option to reduce the storage burden would be for clinics without the ability to store three months worth of ARTs at once to devise alternative ART delivery mechanisms. One potential option would be for their ART supply to be delivered to a larger, centralized facility capable of storing more drugs and then distributed to the smaller facilities in smaller, more manageable batches. This option would require an additional layer of coordination and monitoring to ensure consistent delivery. Further, given that this strategy would not require MCH clinics to conduct viral load monitoring by relying on referrals to ART clinics every two years, this strategy would not require increased laboratory infrastructure solely for the purposes of PMTCT. Finally, Malawi already has a monitoring system in place to keep track of utilization, loss-to-follow up, as well as procedures in place to manage ART drug supplies. However, given the expanded scope of the MCH clinics, these monitoring systems should be strengthened to ensure better tracking of patients, adherence levels, and overall clinic performance.

The additional client burden at MCH clinics could have the unintended consequence of overburdening MCH clinics and actually detract from providing the main services for which they are designed. Further, although Malawi has demonstrated that integration of ART into MCH clinics can be successful, at least for initiation and throughout pregnancy, women may still fall out of treatment or become non-adherent no matter where they are provided their ART. Integration into MCH clinics could also have the unintended consequence of developing two competing systems – one for men and another for women. Alternatively, the fact that complete integration of ART into MCH clinics will increase the number of facilities offering lifelong ART might call into question why separate treatment locations were needed for men and women. While the accessibility of such clinics to male household members of pregnant women could serve as a mutual support for treatment adherence or sharing the burden of drug collection, it would also significantly alter the structure of the clinics. If PMTCT services are implemented within primary health care clinics then extending access to men in those locations may not be a problem. If, however, the MCH clinics providing PMTCT services were more specialized and separate then it would likely be difficult to expand ART services to men without significant alteration to the clinic structure.

Strategy 2: Household Access to Treatment

A second implementation strategy would be the expansion of Option B+ to include individuals living with HIV within the household of a woman initiating Option B+. Access to HIV-testing and treatment for household members under this strategy would rely entirely on current healthcare infrastructure and community-based mechanisms. Further, such a strategy would not guarantee treatment for household members, but rather would make them automatically eligible for treatment regardless of their CD4 count or stage of disease. Only in locations with treatment waiting lists for people currently eligible for treatment would household members of

pregnant women not be initiated on treatment immediately. This strategy, therefore, would not prioritize treatment for household members of pregnant/breastfeeding women over individuals in the community who know their HIV-positive status and are eligible and seeking treatment. In areas without a waiting list, household members would be placed on treatment immediately.

This strategy implicitly has two components. The first is what traditional infectious disease programs refer to as “active case finding”. Looking for previously undetected HIV-infected individuals in the households of identified HIV infected individuals makes sense because the HIV prevalence in such households is high relative to the rest of the population. For example, in one study, 71% of participants reported that there was at least one other member of their household known to be HIV-positive.⁴⁶ Many of the individuals living with HIV identified through active case finding will be eligible for treatment under existing guidelines either because they have a CD4 count ≤ 500 , they are in a sero-discordant relationship, or they are children younger than 5 years.

The other component of the strategy is expanding the eligibility criteria to include any household members who are not eligible under the current guidelines. We do not know what proportion of the individuals in the households of HIV-positive pregnant/breastfeeding women not eligible based on the CD4 criterion would already be eligible based on one of the other criteria. At the level of the entire population, an estimated 28% of individuals living with HIV in Malawi currently do not qualify for treatment based on CD4 criteria (a reported 798,000 eligible for treatment in 2014 and an estimated 1.1 million individuals living with HIV in Malawi²⁹) so this a reasonable upper bound. As countries move towards ever more inclusive eligibility criteria, it seems appropriate to prioritize outreach to household members because of evidence suggesting that household level treatment can improve adherence.⁴⁶

Effectiveness

The logic by which the expansion of Option B+ to a pregnant woman’s household could increase PMTCT program effectiveness is that assured household-level treatment would facilitate increased disclosure rates within families, improve male partner involvement in service utilization, and provide women with a household-level support group. The availability of treatment, regardless of stage of disease, to all members in a household living with HIV could help reduce the fear associated with diagnosis by reinforcing that HIV is a treatable condition. In an environment where pregnant/breastfeeding women are eligible for immediate ART but their male partners are not, there exists the possibility of perceived inequity leading to an increase in intimate partner violence and abandonment of the woman, something women fear simply by disclosing their status.^{47,48,49} Therefore, this strategy would provide pregnant women and their families a positive incentive to openly discuss HIV-testing results, which could increase disclosure rates and in turn, adherence. This strategy, however, is highly reliant on women’s own willingness and readiness to disclose.

Pregnant women who disclose their HIV-positive status to others are much more likely to adhere to HIV care and treatment than women who do not.^{50,51,52,53,54} Disclosure allows a

woman to freely communicate why she needs to go to the clinic and why she has to take medication. However, in areas where HIV-infection is highly stigmatized, fear of violence, abandonment, or other negative repercussions can inhibit disclosure.^{47,48,49} A systematic review that included 47 studies reported a pooled estimate of 67% disclosure among pregnant women living with HIV.⁵⁵ The range of disclosure reported within the studies varied, however, from 5% to 97%. Therefore, identifying a mechanism to further increase disclosure rates could facilitate even greater levels of adherence.

Disclosure also enables partner involvement, which is another mechanism through which better outcomes have been observed.^{56,57,58} For example, a cohort study found that women whose male partner attended ANC with them had 42% lower risk of infant infections than women whose partner did not attend.⁵⁹ Much like disclosure, male partner involvement allows couples to make decisions together and to openly communicate about service utilization and practices to reduce transmission, regardless of the sero-status of the male partner. However, when clinic schedules and service provision are not conducive to male engagement, their involvement can be difficult to encourage or sustain.⁶⁰ Disclosure in sero-discordant couples, even in absence of treatment, has been shown to reduce transmission to the uninfected partner.^{61,62} Sero-discordant couples that do disclose can be expected to significantly improve ART adherence because both partners are motivated by self-interest to maintain high levels of adherence.

Finally, by treating the household as a unit for treatment, the household can serve as a support group holding each other accountable for adhering to treatment and ensuring the best health outcomes for all, regardless of the sero-status of the other household members. Studies show that adherence rates improve when ART patients have a support system.^{63,64} For example, a study examining community-based adherence clubs, which served not only as educational and support groups, but also allowed participants to share the burden of retrieving the group's drugs, observed 98% adherence over a 12 month period.⁶⁵ Family-centered approaches have also been shown to increase outcomes.⁶⁶ Byakika-Tusiime *et al* found that when everyone eligible for ART in a household received treatment all household members had reported adherence above 98%.⁴⁶ Fostering support groups already existing within households would be a valuable complement to other community-based or clinic-based support groups.

Despite the potential positive associations increased disclosure could have on improving treatment adherence among women initiating Option B+, the possibility of negative or violent reactions is real. This strategy, however, will not provide any additional encouragement for women to disclose their status beyond the educational and support information provided to individuals during pre- and post- HIV-test counseling. Information about the expanded access to Option B+ to household members would only be an added piece of information shared during these sessions and would not be used as a forcing mechanism for women to disclose. In the event that a pregnant or breastfeeding woman discloses her status to her household members and is the only individual living with HIV within the household there is the potential for increased isolation. However, the benefits of disclosure, regardless of the sero-status of others, remain. Additionally, should her partner be HIV-negative, the mutual awareness of their

respective HIV-status should still facilitate greater adherence in order to reduce the likelihood of transmitting HIV not only to the infant, but to her partner.

The strategy of expanding access to ART to the household members of a woman initiating Option B+ has additional benefits beyond the potential to improve adherence among pregnant/breastfeeding women. Specifically, the inclusion of a woman's household in Option B+ programming would help to identify individuals living with HIV who might not know their status or are not accessing HIV care and treatment services. For example, in Malawi, 27% of women and 48% of men have never been tested for HIV,²⁷ and only 40% of men report having received an HIV test and its result in the previous 12 months.²⁹ Additionally, UNAIDS estimates that globally only 48% of individuals living with HIV know their status. However, once aware of their status, uptake of treatment is relatively high. In Sub-Saharan Africa, UNAIDS claims that roughly 86% of individuals who are aware of their status and eligible for treatment, are receiving ART.¹ Even if that estimate is overly optimistic, it emphasizes that effective treatment is only possible with timely diagnosis. Additionally, this strategy could help to reduce the high rates of attrition from HIV-testing to initiation of ART, especially among individuals not yet qualifying for treatment at the first CD4 test.^{67,68} It is estimated that in low-income countries a quarter of individuals initiating ART do so when their CD4 count is below 100 cells/ml (not considering those who die without ever initiating),⁶⁹ levels at which individuals are very sick and have much lower survival rates. Therefore, this strategy could have a much broader impact for both preventing and treating HIV infections beyond improving PMTCT outcomes. By treating a household as the unit accessing treatment, no individual living with HIV in the household would be prioritized over another person.

Despite the potential benefits, this strategy may place individuals on treatment who are not yet ready to commit to being on treatment for the rest of their lives. Should these individuals start treatment but later default, they could develop drug resistance and have a much more difficult time in the future lowering their viral load. Although examination of understanding and willingness to commit to lifelong ART is part of standard clinical procedures prior to ART initiation, even closer monitoring may need to take place to reduce loss-to-follow up. Additionally, by having other household members aware of their status and the intra-household support mechanism provided by at least the pregnant/breastfeeding woman in the household, adherence could remain high.

Equity

This strategy would increase treatment equity within a woman's household. The inclusion of a woman's household in Option B+ programming would help to better identify individuals living with HIV who might not know their status or are not accessing HIV care and treatment services. By treating a household as the unit accessing treatment, no individual living with HIV in the household will be prioritized over another person. Conversely, this strategy could exasperate feelings of exclusion for those families without a pregnant woman or have the unintended consequence of encouraging families to get pregnant when they might not want to simply to become immediately eligible for treatment. Additionally, with only 28% of individuals in Malawi living with HIV not currently eligible, and half of all individuals living with HIV already receiving

treatment, such negative repercussions should be minimal. Further, it may actually serve as a motivator for individuals to not only learn their HIV-status if they are unaware, but also to receive a CD4-test and its result to determine their treatment eligibility.

Maximize Available Resources

Malawi's commitment to striving to reach the UNAIDS 90-90-90 targets, will require the country to further scale up access to treatment. The expansion of Option B+ to include household members of pregnant/breastfeeding women would be one mechanism Malawi could utilize to make progress towards this goal. Although this strategy will increase the number of individuals seeking treatment, Malawi is already budgeting for and hoping to reach 90% of individuals living with HIV who are aware of their status on treatment. Therefore, this strategy would work within Malawi's anticipated budget, instead of adding to it. This strategy has the added benefit of reducing the burden placed on the health system to conduct outreach to identify individuals living with HIV who are unaware of their status, and provides a targeted, network approach to connecting known positive individuals to treatment programs.

The sustainability of this strategy is in large part due to the fact that as more individuals are on treatment, transmission to sexual partners and children will decrease and therefore reduce the numbers of individuals needing treatment in the future. However, we must also recognize that this strategy may only limit further transmission among individuals at lower risk for continued transmission. Pregnant women accessing services may be more likely to be in stable, monogamous partnerships. The prevention benefits in such relationships would only extend to a sero-discordant partner and the infant, much less than targeted treatment of higher-risk individuals who have multiple sexual partners or individuals engaged in sex work. However, 67% of all new HIV infections in Malawi are estimated to occur within married/cohabitating heterosexual partnerships,²⁹ so the prevention benefits, and cost-effectiveness, of this strategy could still be quite high.

There is a logical inconsistency in global guidelines that prioritize ART for individuals living with HIV in sero-discordant relationships over people living with HIV with multiple sexual partners of unknown HIV status, but that is beyond the scope of this analysis.

Feasibility

This strategy would work within Malawi's existing healthcare infrastructure, which is already equipped to handle routine HIV-testing and treatment. Although this strategy will increase utilization of these services, Malawi has already planned to scale up access to both HIV-testing and treatment. Therefore, this strategy should face minimal political resistance.

The success of this strategy depends heavily on increasing communications within families about the importance of knowing your HIV-status and what this policy shift could mean for them. Pre- and post- HIV-test counseling already include information about the importance of disclosing ones' status, male partner involvement, and support mechanisms available at the clinic and in the community. Information about the availability of treatment for household members also living with HIV would simply need to be added to the counselor's script. This

strategy would also benefit from Malawi's ongoing campaigns across various media to reduce stigma and increase awareness about HIV prevention and treatment.

There are also a number of potential unintended consequences of the household treatment strategy. First, this strategy develops yet another group of individuals eligible for treatment. The case for why these individuals should become automatically eligible for treatment might be more difficult to justify if everyone else who is currently eligible for treatment and aware of their status is not able to access treatment. However, nearly three-quarters of all individuals living with HIV in Malawi are eligible for treatment under the 2013 guidelines and by the end of 2014 Malawi had 67% of eligible individuals on treatment. Additionally, with the current treatment guidelines expanding eligibility to individuals in sero-discordant partnerships, the number of individuals not qualifying for treatment on their own is likely even smaller. Second, if the uptake of this strategy results in high volumes of individuals receiving HIV tests, learning their HIV-positive status, and subsequently initiating treatment, HIV care and treatment services might be unable to adequately respond to such an influx. The healthcare system would first need to ensure that they are able to provide a high standard of care to individuals already on treatment before further expanding access.

Finally, the largest drawback to this strategy would be Malawi's ability to support the expansion of ART eligibility. Malawi's aspirations of meeting the UNAIDS 90-90-90 treatment targets highlights the importance Malawi is placing on scaling up treatment coverage for both the therapeutic and the preventative benefits. Although Malawi has plans to increase ART coverage, their programming is almost entirely dependent on foreign support. Further, Malawi currently has a potential 43% budget shortfall between their anticipated expanded national HIV activities and the promised resources.²⁹ Should the next round of Global Fund support not be approved, and the rapid expansion of treatment coverage not possible, the household strategy could be a mechanism through which Malawi is able to still scale up treatment coverage, but through a more targeted, and less costly approach. If no additional funding is mobilized from international donors, Malawi may have to rethink their plans to further expand ART coverage.

Assessing the Trade-Offs

Regardless of which Option B+ implementation strategy Malawi utilizes, there is an opportunity for improvement. The two strategies presented in this paper are just two of a number of different ways Option B+ could be implemented to improve PMTCT effectiveness. Although both strategies will require additional funding and health staff to manage an increase in the potential number of individuals seeking or continuing care, the costs associated with Option B+ programs with high loss-to-follow-up or non-adherence to treatment could result in greater costs to the system in the future. Following the successful implementation of Option B+, Malawi must now turn to improving adherence among women initiating ART under Option B+.

The two strategies presented here are not mutually exclusive. They utilize different mechanisms to improve adherence and are non-competing. In fact, the implementation of both could have additive impact. For example, should women continue to attend MCH clinics to

receive ART and their household members also access treatment, long-term adherence both for the woman and her household members could significantly improve. Not only would women have a more convenient and less stigmatized place to receive regular treatment, but the intra-household disclosure and support mechanisms would also improve adherence. Further, if pregnant/breastfeeding women continue to receive ART at MCH clinics, the ART specialty clinics would have a greater capacity to attend to household members seeking care. However, the ability to implement both strategies would depend on Malawi's ability to mobilize and retain sufficient number of nurses and other health staff to provide and monitor adherence for all individuals initiating ART.

While they both have the potential to increase ART adherence, the household strategy has the potential to have a more significant impact on the HIV-epidemic. Not only should adherence improve among women initiating ART during pregnancy/breastfeeding, but the potential for more individuals to learn their HIV-status and initiate treatment would facilitate Malawi's efforts to strive for the UNAIDS 90-90-90 treatment targets. The preventive benefits of more individuals on treatment could also help to further decrease HIV-incidence in the country. However, the household strategy would require Malawi to have the funding available to further scale up access to ART. If they were not able to secure additional funding for ART then the household option would be less feasible than the MCH clinic strategy.

Further, the MCH clinic strategy might be implementable more quickly. Given that MCH clinics already initiate women on ART and receive quarterly ART deliveries, the expansion of ART to lifelong provision at MCH clinics might require fewer shifts in operating procedure than the expanded access of ART to household members. The household strategy would take more time to implement because of its expanded scope. Specifically, it would require 1.) a more extensive review by key stakeholders to approve of this strategy as a mechanism to increase treatment coverage by creating another eligibility group, 2.) time to secure the funding needed to expand ART coverage, and 3.) updated media and educational materials to inform pregnant/breastfeeding women and the general population about the policy shift.

Conclusion

Malawi's successful implementation and expansion of Option B+ decreased mother-to-child HIV transmission rates by 67% since 2009.¹ While such achievements are remarkable, placing all pregnant and breastfeeding women on lifelong ART requires ardent attention to achieving high levels of adherence, not only while the infant is at risk for infection but also to improve the health of the mother. Early evidence indicates that long-term adherence is sub-optimal.

We proposed two strategies that Malawi should consider implementing to increase the effectiveness of their PMTCT program. Given what we know, both strategies appear as though they could be effective and feasible within the current healthcare infrastructure. However, both strategies warrant additional analysis on finer points of the health system capabilities prior to implementation. Should such analyses further support the feasibility of these options then Malawi could move forward with implementation. Regardless, failure to improve long-term

adherence levels within Malawi's PMTCT program will result in higher levels of pediatric HIV infections, increased development of drug resistance, and poorer health outcomes for mothers, their sexual partner(s) and their children. In addition to their efforts to further expand access to ART, Malawi must now turn their attention to improving adherence.

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Conclusion

The objective of this dissertation was to explore factors influencing the utilization of prevention of mother-to-child HIV transmission (PMTCT) services and to propose potential policy alternatives to improve long-term adherence to PMTCT programs. I achieve this objective through the work of the three distinct papers summarized below.

The first paper was a secondary data analysis utilizing serial cross-sectional data collected for the impact evaluation of Zimbabwe's national PMTCT program. This paper explored the association of costs (service costs, travel time, and transportation costs) with utilization of all of the recommended services for pregnant women living with HIV (4 antenatal care visits, a CD4 test and its result, facility delivery, maternal antiretroviral drugs (ARVs), infant ARVs, and an infant HIV test). Within this study population there was no association between complete service utilization and services costs or between complete service utilization and transportation costs. These findings were contrary to expectation. However, the findings could highlight that even in the presence of costs for services, utilization of all PMTCT services is inelastic because of the importance women place on preventing the transmission of HIV to their infants. Travel time, however, was significantly associated with a lower probability of receiving all six recommended services. While the finding that increased travel time is a barrier to PMTCT service utilization is not unexpected, it does highlight how detrimental time and distance can be on women's willingness and ability to utilize services. Mechanisms to reduce this burden could be to increase the utilization of mobile clinics, provide or subsidize transport, or increase the number of clinics offering PMTCT services to reduce the distance required to travel to obtain PMTCT services.

The second paper utilized the same data as the first paper, but examined the association between the timing of a woman's HIV-positive diagnosis relative to her pregnancy, either prior to or during her pregnancy, and three levels of service utilization (zero, some, and all). The three-level outcome variable captured utilization of the following PMTCT services: CD4 test, maternal ARVs, infant ARVs, and an infant HIV test. This was the first study to explore this association within a large sample of women living with HIV and to examine the association beyond a single service. The results showed a dramatic increase in service utilization of each of the services between 2012 and 2014. They also revealed increased utilization among women who were diagnosed prior to pregnancy between 2012 and 2014. However, in 2012 women diagnosed prior to pregnancy were less likely to have completed some or all of the services compared to women diagnosed during their pregnancy. This association reversed in 2014, with women diagnosed prior to pregnancy more likely to complete some or all services than women diagnosed during pregnancy. With PMTCT drug regimens now requiring women to be engaged with the health system for a much longer period of time, specialized counseling, support, and follow-up mechanisms adapted to fit the different needs of women diagnosed prior to or during pregnancy should be developed to improve retention in PMTCT programs going forward and thereby improve overall outcomes.

The final paper utilized a policy analysis approach to examine the outcomes of two proposed strategies to improve lifelong adherence to antiretroviral therapy (ART) among women

initiating treatment during pregnancy or breastfeeding for PMTCT in Malawi. The two strategies explored were: 1) for all pregnant/breastfeeding women to initiate and indefinitely receive treatment at maternal and child health clinics rather than be transferred to an ART specialty clinic, and 2) to offer the option to initiate lifelong ART, regardless of stage of disease, to any individual living with HIV in the pregnant/breastfeeding woman's household. Both strategies appear to be feasible within Malawi's healthcare infrastructure and to have the potential to increase ART adherence among women initiating treatment for PMTCT. However, both strategies warrant additional and more detailed analyses on the health system capabilities prior to implementation. Only in the instance where the additional analyses confirm the feasibility of one or both of these strategies should Malawi proceed with implementation. Further, the world continues to move towards universal access to treatment due to the increasing evidence about the preventive and therapeutic benefits of earlier treatment initiation. However, programs will still need to prioritize efforts to increase treatment coverage and maintain optimal adherence among those most at risk for transmission. Therefore, even as more countries shift to universal treatment access, the proposed strategies in this paper still have the potential to improve treatment adherence and to identify individuals unaware of their status and connect them to treatment.

Together, the results of the three papers add to the growing body of evidence around the proximal and distal factors associated with increased or decreased utilization of PMTCT services. As access to testing and treatment become less of an issue, retention in PMTCT services and adherence to treatment regimens will be the main drivers of improved program effectiveness and maternal/pediatric outcomes. The findings of each of these papers, separately and together, can help PMTCT programming going forward to remove barriers to utilization, improve outcomes, and save lives.