ORIGINAL ARTICLE

Outcomes of HIV-Exposed Infants enrolled in the Prevention of Mother to Child Transmission of HIV (PMTCT) Program in Philippine General Hospital: An 8-year Retrospective Study

Anna Soleil Cheshia V. Tan, MD, DPPS
Marimel R. Pagcatipunan, MD, FPPS, FPIDSP

Division of Infectious and Tropical Diseases in Pediatrics
Department of Pediatrics
University of the Philippines-Philippine General Hospital

Correspondence:
Dr. Anna Soleil Cheshia V. Tan
Email: annatan686@gmail.com

The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

1ST PRIZE 2021 PIDSP RESEARCH CONTEST

ABSTRACT

Background: Our country has the fastest growing number of HIV cases in the Asia-Pacific region with a 203% increase from 2010 to 2018. MTCT represents 6% of infections in children and interventions such as the PMTCT program are essential to help reduce new infant infections.
Objective: To determine the outcomes of HIV-exposed infants born in PGH from 2010 to 2018 enrolled in the PMTCT program. To analyze the association of maternal and neonatal clinicodemographic factors to MTCT of HIV.
Methods: A retrospective cohort study using data collected from medical records of HIV exposed infants enrolled in the program.
Results: Out of 117 mother-infant pairs, only 70 met the eligibility criteria. Maternal factors showed that majority have: timely antenatal visit (56/70), maternal HIV diagnosis (70/70) and ART initiation (67/70) prior to delivery, triple lifelong maternal ART (69/70), CD4 >200 prior to delivery (52/70) and cesarean delivery (67/70). Amongst the infant factors-early infant prophylaxis (60/62), >4weeks prophylaxis duration (62/70) and replacement feeding (62/70) were noted in the majority. 2/70 infants were HIV positive. Mortality rate was 1.4% and 50% for HIV infected infants. Overall LTFU rate was 33.3%. Logistic regression showed that maternal co-infection with Hepatitis B(p=0.0275) was a possible determinant of MTCT. Infant HIV prophylaxis duration of >4 weeks had higher survival proportion(p=.0001).
Conclusion: The HIV MTCT rate was 2.86% upon implementation of our PMTCT program, meeting the <5% goal of WHO, suggesting that the program was an effective health intervention strategy. The high LTFU rate though should be considered in the evaluation of the program effectiveness.

KEYWORDS: *PMTCT, HIV-Exposed Infant, ARV prophylaxis, HIV Philippines*

INTRODUCTION

Global statistics as of 2018 reported 37.9 million people living with Human Immunodeficiency Virus (HIV), 1.7 million of which are children less than 15 years old and a total of 1.7 million new infections were recorded.[1] While the prevalence of HIV and Acquired Immunodeficiency Syndrome (AIDS) in the Philippines is still low, our country has the fastest growing number of cases in the Asia-Pacific region with a 203% increase from 2010 to 2018.[1] Mother to child transmission (MTCT) represents 6% of acquired infection in children and adolescents.[2] MTCT of HIV refers to vertical transmission of HIV from an HIV-positive mother to her baby at one or more of the following stages: pregnancy, labor, delivery or breastfeeding. The following are integral components of Prevention of Maternal to Child Transmission (PMTCT): primary prevention of HIV, especially among women of childbearing age; preventing unintended pregnancies among women living with HIV; preventing HIV transmission from a mother to her infant; and providing appropriate treatment, care, and support to women living with HIV and their children.[3] Locally, the applicability and effectiveness of these programs are not known and there is limited information on maternal and infant outcomes.

In the absence of any intervention, MTCT rates range from 15% to 45%.[3,4] This rate can be reduced to below 5% in breastfeeding populations and below 2% in non-breastfeeding populations[5] with interventions such as the PMTCT program. "Elimination" of pediatric HIV is the ultimate goal, defined as 90% reduction of new infant infections and a decrease of MTCT to <5%.[6] Antiretroviral therapy (ART) has been proven effective in reducing rates of MTCT of HIV. In resource-limited countries, about 35% and 52% of HIV infected infants without any therapeutic intervention die by age one and two respectively.[7] Variability in prophylactic regimens remains and consistency with guideline implementation has not been evaluated in the Philippines. Several studies reported on the effectiveness and outcomes of the PMTCT program in other countries;[4,6,8-11] currently there are no published data in the Philippines. It is important to monitor the efficacy and uptake of the PMTCT program as HIV cases; along with the number of HIV exposed infants are increasing every day.

This study aims to determine the outcomes of the PMTCT program among HIV-exposed infants born in the Philippine General Hospital (PGH) from 2010 to 2018 and determine association of maternal and neonatal clinic-demographic factors to MTCT. Specifically, this study will evaluate the following outcomes of women-infant dyads enrolled in PMTCT: HIV transmission rate, infant survival and other morbidities. Likewise, to determine the association of maternal and neonatal factors with HIV infection among exposed infants. Factors to be analyzed are: maternal demographics, timing of maternal diagnosis and initiation of treatment, maternal ARV treatment and duration, maternal viral load and CD4+ lymphocyte count, manner of delivery, maternal co-infections, pediatric age at birth, size for gestational age and birth weight, type of feeding, initiation, duration and type of infant ARV prophylaxis.

METHODOLOGY

Retrospective cohort design was used to investigate the outcomes of the PMTCT program. Total enumeration of cases was done. The study included all infants born to HIV-infected mothers who delivered at the Philippine General Hospital from January 1, 2010 to December 31, 2018 and subsequently referred to the Division of Infectious and Tropical Diseases in Pediatrics (INTROP), enrolled in the PMTCT program and seen on follow up at the STD/AIDS Guidance Intervention Prevention Unit (SAGIP) Clinic. HIV-exposed infants were excluded if they were not delivered/born in PGH, infants aged 18 months or above and infants who do not have two virological tests done.

HIV-exposed infants were identified using INTROP and SAGIP charts/case records. Corresponding neonatal and maternal charts were retrieved as needed from PGH Medical Records Section. Information on maternal and neonatal clinico-demographic factors were recorded. The primary endpoint of this study was the outcome of the program, specifically, HIV transmission rate, infant survival and other related co-morbidities. Maternal and neonatal factors were also evaluated in association with HIV transmission.

Operational Definitions

ARV prophylaxis: short term use of ARV drugs in the mother and/or infant to reduce MTCT.[12]

ART: the use of 3 or more ARVs drugs simultaneously to treat HIV infection.[12]

Mixed feeding: alternation of replacement feeding and breast milk in the first six months or by substitution of breastfeeding with formula before six completed months of life.

HIV Infected infant: if the infant has a positive RNA-PCR test,[13,14] if the first test is positive, we label as "HIV infected infant" pending 2nd PCR.

HIV-Exposed, Uninfected infant: if the infant has 2 negative RNA-PCR tests.[13-15]

Loss to Follow-up: a period of more than 3 months without a visit for children receiving ARV prophylaxis or a period of more than 6 months without a visit for those not receiving ARV prophylaxis.[16]

Data Analysis

For descriptive analysis, maternal and infant variables were summarized as frequency and percentage distributions. Since the sample size turned out to be smaller than expected, and certain cells had small counts, the Fisher's exact test was used to determine the association between HIV transmission and maternal and neonatal factors. Logistic regression analysis was used to show the individual and simultaneous effects of maternal and infant factors on the risk of MTCT of HIV. A 5% level of significance or a p value of <0.05 was used in testing the hypotheses. Infant survival was evaluated based on Kaplan Meier Estimate.

Ethical Considerations

The study was submitted to the University of the Philippines Manila Research Ethics Board for approval prior to data collection. A waiver of informed consent was requested from the ethical panel in accordance to the National Ethical Guidelines of Health and Health-related Research 2017. A written informed consent was obtained from the parents/guardians upon admission/birth of the patient and upon enrollment in SAGIP. The principal investigator solely collected the data. All data gathered were anonymized using numerical and alphabetical codes, kept strictly confidential and filed in a secured cabinet. Soft copy of the files utilized password encryption saved in a USB storage device. The data will be stored for at least ten years from the date of final publication and will be destroyed thereafter. In case of breach to data privacy, matter will be forwarded immediately to the PGH data privacy officer. The investigator declares that there is no conflict of interest in the pursuit of this study. Researchers are not associated with any sponsor nor received any incentive for doing the study.

RESULTS

A total of 117 mother-infant dyads were enrolled in the PMTCT program from January 2010 to December 2018 (Figure 1).

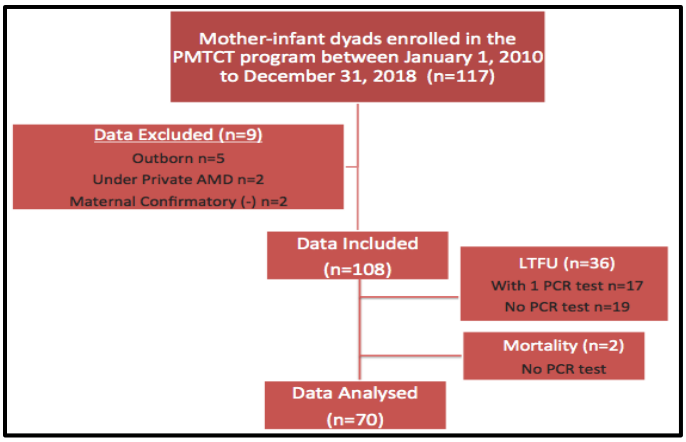

Figure 1. Population Flowchart/Process of Record

Considering the eligibility criteria, only 70 mother-infant pairs were included from the point of antenatal enrollment to birth until follow up visits. Maternal data (Table 1) showed that majority of mothers were between 18 to 35 years old, single, multi-gravid and finished secondary school. More than half 61.4% (43/70) were employed and 18.6% (13/70) were sex workers. The most common route of HIV transmission noted was through sexual contact, wherein 45.7% (32/70) of mothers had multiple partners and 40% (28/70) reported HIV positive partners in which 14.3% (10/28) of them were men having sex with men (MSM). Other modes of transmission included: domestic/sexual abuse (2.9%), having a high risk/promiscuous partner (4.3%) and blood transfusion (2.9%). Prenatal history revealed that majority had their first antenatal visit during the first trimester and were diagnosed and started on ART during pregnancy. 98.6% (69/70) of mothers were prescribed with lifelong ART with lamivudine (3TC), tenofovir (TDF) and efavirenz (EFV) being the most common choice, followed by 3TC, zidovidine (AZT) and lopinavir/ritonavir (LPV/r). Moreover, 18.6% (13/70) were classified as HIV Clinical Stage 3 and 4 and the most common co-infection was sexually transmitted infection (STI) / lower genital tract infection (18.6%). Diagnostic evaluation showed that 87.2% (61/70) had CD4 count (mean= 406.3 cells/mm^3) results prior to delivery, however, viral load determination was not routinely done. Intrapartum management showed majority delivered via cesarean section.

TABLE 1. Maternal Demographics

Variables	N=70 (%)
Age	
≤17 years old	0 (0.0)
18 to 35 years old	58 (82.9)
>35 years old	12 (17.1)
Marital Status*	
Single	44 (63.8)
Married	25 (36.2)
Obstetric Score	
Primigravid	20 (28.6)
Multigravid	50 (71.4)
Educational Attainment	
Primary	1 (1.4)
High School	41 (58.6)
College Level/Graduate	19 (27.1)
Vocational Course	9 (12.9)
Occupation	
Unemployed	27 (38.6)
Employed	43 (61.4)
Sex Worker	13 (18.6)
Reported Transmission Route	
Multiple Partners	32 (45.7)
Positive Partner	28 (40.0)
Men Having Sex with Men	10 (14.3)
IV drug user/Sharing needles	4 (5.7)
Unknown/No answer	15 (21.4)
Others	7 (10.0)
Domestic/Sexual Abuse	2 (2.9)
Having a high-risk partner	3 (4.3)
Blood Transfusion	2 (2.9)
HIV Status of Partner	
Positive	28 (40.0)
Negative	6 (8.6)
Unknown	36 (51.4)
First Antenatal Visit	
First trimester	56 (80)
Second trimester	14 (20)
Third trimester	0 (0.0)
Timing of HIV Diagnosis	
Before pregnancy	30 (42.9)
During pregnancy	40 (57.1)
First Trimester	9 (12.9)
Second Trimester	17 (24.3)
Third Trimester	14 (20.0)
After giving birth	0 (0.0)
Maternal ART Initiation	
Before pregnancy	20 (29.9)
During pregnancy	47 (67.1)
First trimester	8 (11.4)
Second trimester	18 (25.7)
Third trimester	21 (30.0)
After giving birth	3 (4.3)
Maternal ART given	
Single/Dual therapy	1 (1.4)
AZT + 3TC	1 (1.4)
Triple therapy	69 (98.6)
AZT + 3TC + LPV/r	10 (14.3)
AZT + 3TC + EFV	4 (5.7)
AZT + 3TC + NVP	3 (4.3)
TDF + 3TC + EFV	51 (72.9)
TDF + 3TC + NVP	1 (1.4)
None	0 (0.0)
WHO Clinical HIV Disease Stage	
Stage 1	56 (80.0)
Stage 2	1 (1.4)
Stage 3 and 4	13 (18.6)
Maternal Co-infections	
STIs/ Lower Genital Tract Infections	13 (18.6)
Pneumocystis jirovecii pneumonia	2 (2.9)
Tuberculosis	8 (11.4)
Hepatitis B	3 (4.2)
Candidiasis	4 (5.9)
Others	2 (2.9)
CD4 Count**	
< 200 cells/mm^3	9 (12.9)
200-499 cells/mm^3	32 (45.7)
>500 cells/mm^3	20 (28.6)
Not done/Unknown	9 (12.9)
Viral Load**	
< 50 copies/mL	15 (21.4)
50-1000 copies/mL	1 (1.4)
>1000 copies/mL	4 (5.7)
Not done/Unknown	50 (71.4)
Mode of Delivery	
Spontaneous Vaginal Delivery	3 (4.3)
Cesarean Section	67 (95.7)

**n=69, 1 maternal chart has no data*
***done during pregnancy*

Infant data (Table 2) showed that majority are male, delivered term and appropriate for gestational age with birth weight of ≥2500 grams. ARV prophylaxis was started within 12 hours of life in 96.8% (60/62) of infants. Duration of prophylaxis varied from 7 days, 4 to 6 weeks and more than 6 weeks. The antiretroviral/s prescribed was: single drug prophylaxis with nevirapine (NVP) or AZT, dual therapy with AZT and NVP and triple prophylaxis using 3TC+AZT+NVP. Majority of the infants were given replacement feeding. HIV PCR testing was done twice at 4 to 6 weeks and 4 to 6 months of life in most of the infants. Cotrimoxazole prophylaxis was given to all infants. Moreover, 11.4% (8/70) were given isoniazid prophylaxis due to exposure to tuberculosis in the household. Only 38.6% (27/70) of infants have completed vaccination up to 9 months. Majority of the infants had an unremarkable neonatal course. Neonatal comorbidities were prematurity (18.6% or 13/70), infection (20% or 14/70), specifically neonatal

pneumonia and sepsis and congenital anomalies (5.7% or 4/70). One infant had an allergic reaction to nevirapine.

TABLE 2. Infant Demographics

Variables	N=70 (%)
Gender	
Male	43 (61.4)
Female	27 (38.6)
Pediatric Age at birth	
<28 weeks	0 (0.0)
28-32 weeks	0 (0.0)
33-36 weeks	13 (18.6)
≥ 37 weeks	57 (81.4)
Size for Gestational Age	
Small for Gestational Age	5 (7.1)
Appropriate for Gestational Age	65 (92.9)
Large for Gestational Age	0 (0.0)
Birth Weight	
< 1000 grams	0 (0.0)
< 1500 grams	0 (0.0)
1500-2499 grams	17 (24.3)
≥2500 grams	53 (75.7)
Prophylaxis Started*	
Within 12 hours of life	60 (96.8)
Within 24 hours of life	2 (3.2)
> 24 hours of life	0 (0.0)
Duration of Prophylaxis	
≤1 week	5 (7.1)
>1 weeks to ≤4 weeks	3 (4.3)
>4 weeks to ≤6 weeks	46 (65.7)
>6 weeks	16 (22.9)
Antiretroviral Prophylaxis	
Zidovudine alone	15 (21.4)
Nevirapine alone	36 (51.4)
NVP + AZT	6 (8.8)
NVP + AZT + 3TC	13 (19.1)
Feeding Practice	
Breastfeeding	2 (2.9)
Replacement Feeding	62 (88.6)
Mixed Feeding	6 (8.6)
HIV PCR Testing	
4 to 6 weeks and 4 to 6 months	56 (80)
Other Timing	14 (20)
With follow up Serological Test	
Yes	10 (14.3)
No	60 (85.7)
Cotrimoxazole Prophylaxis	
Yes	70 (100)
No	0 (0)
Isoniazid Prophylaxis	
Yes	8 (11.4)
No	62 (88.6)
Vaccination Status (up to 9 months)	
Complete	27 (38.6)
Incomplete	43 (61.4)
Neonatal Comorbidities	
Prematurity	13 (18.6)
Congenital Anomaly	4 (5.7)
Infection	14 (20)
Others	3 (4.3)
None	47 (67.1)

**n=62, 8 neonatal charts had no data on timing of prophylaxis initiation*

Results revealed that only 2 out of 70 subjects or 2.86% (95% CI 0.79% to 9.84%) had MTCT. All the above-mentioned variables were tested and did not show any significant association with MTCT but Hepatitis B infection in mothers was a potential factor (p=.0845). Table 3 highlights the maternal co-infection variables tested for association with MTCT.

TABLE 3. Fisher's Exact Test/Test of Association of Mother-Infant Profile to MTCT

Variables	HIV Positive N=2 (%)	HIV Negative N=30 (%)	*p*-value
Maternal Co-infections			
STIs/ Lower Genital Tract Infections	1 (50.0)	12 (17.6)	0.3391 ns
Pneumocystis jirovecii pneumonia	0 (0.0)	2 (2.9)	1.0000 ns
Tuberculosis	0 (0.0)	8 (11.8)	1.0000 ns
Hepatitis B	1 (50.0)	2 (2.9)	0.0845 ns
Candidiasis	0 (0.0)	4 (5.9)	1.0000 ns
Others	0 (0.0)	2 (2.9)	1.0000 ns

Univariate regression analysis revealed that coinfection with maternal Hepatitis B is a significant risk factor. Specifically, mothers with Hepatitis B were 33 times (95% CI 1.47 to 738.72; p=0.0275) more likely to transmit HIV infection to their infants as compared to those without Hepatitis B. (Table 4). On the other hand, none of the factors turned out to be significant in the multivariate regression run.

TABLE 4. Logistic Regression – Univariate and Multivariate Regression of Maternal and Neonatal factors associated with MTCT

			Univariate Analysis		Multivariate Analysis	
Variables	**HIV Positive n (%)**	**HIV Negative n (%)**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
MATERNAL						
Maternal Co-infections						
STIs/ Lower Genital Tract Infections	1 (50.0)	12 (17.6)	4.67 (0.27 to 79.96)	0.2879	1.94 (0.03 to 131.86)	0.7590[ns]
PCP pneumonia	0 (0.0)	2 (2.9)	-	-	-	-
Tuberculosis	0 (0.0)	8 (11.8)	-	-	-	-
Hepatitis B	1 (50.0)	2 (2.9)	33 (1.47 to 738.72)	0.0275	29.98 (0.35 to 2548.9)	0.1336[ns]
Candidiasis	0 (0.0)	4 (5.9)	-	-	-	-
Others	0 (0.0)	2 (2.9)	-	-	-	-

In terms of infant prophylaxis (Single- 98.08% Survival, Dual-83.33% Survival and Triple-92.86% Survival), figure 2 denotes that the survival rate across the different treatment regimens was not significantly different (Logrank *p* value=0.1816) while length of prophylaxis (Figure 3), that is-- duration of more than 4 weeks had significantly higher survival proportion than those given less than 4 weeks prophylaxis (Logrank *p* value=.0001).

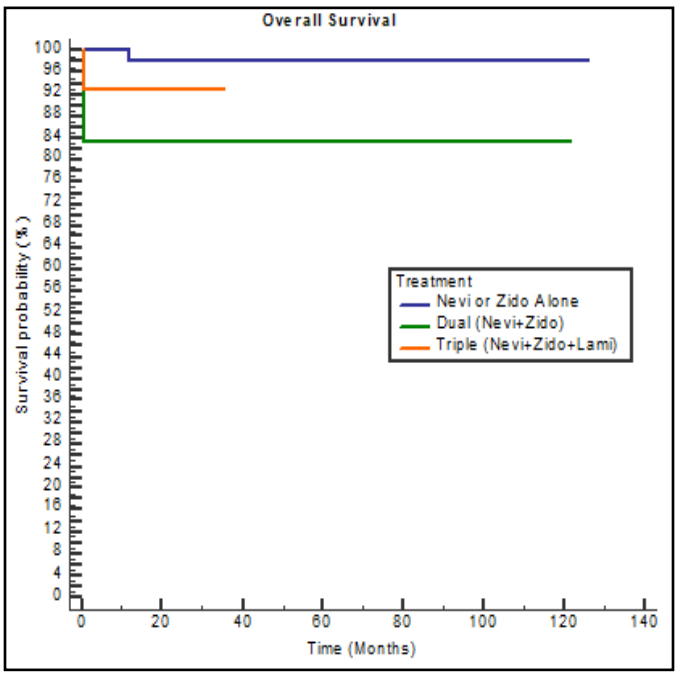

Figure 2. Kaplan-Meier Curve for Infant survival with single vs. dual vs. triple ARV prophylaxis

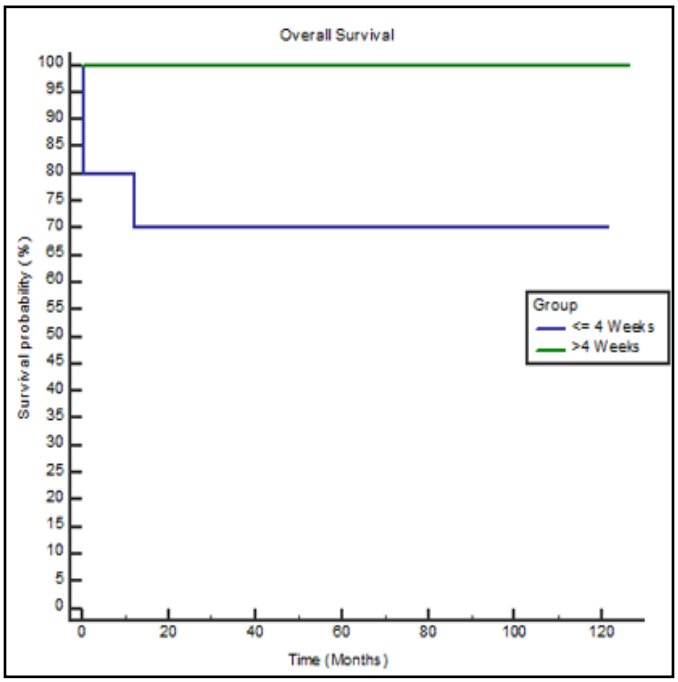

Figure 3. Kaplan-Meier Curves for Infant survival with ≤ 4 weeks vs. > 4 weeks duration of infant ARV prophylaxis

DISCUSSION

An effective PMTCT program is essential to eradicate MTCT of HIV in resource-limited countries such as the Philippines. The vital first step is early identification of mothers with HIV, which serves as the entry point to the program. We noted that majority of cases were enrolled during the later years (2016-2018) representing 65.7% of included pairs. Around this time, our institution was able to procure HIV Rapid Test kits and the DOH began to offer free HIV testing in health centers for pregnant women. These factors may have influenced a higher rate of maternal HIV detection and enrollment during 2016-2018 resulting in an increase in the number of HIV exposed infants.

The MTCT rate of HIV infection among exposed infants in this study was 2.86%. There is no available data on the national rate of MTCT, but according to the DOH 2020 HIV Registry,[2] 196 out of 3,349 pediatric cases from 1984-2020 acquired HIV through vertical transmission. Theoretically, the rate is estimated to be 15% to 45% without PMTCT intervention.[4] Regional rate for Asia and the Pacific is 21%.[1] Hence, a rate of 2.86% demonstrates that our interventions were probably effective. However, if we account for LTFU infants including the 2 mortalities with no virological test, worst-case scenario MTCT rate would be 37% (40/108). Thus, our rate might not be a true reflection of MTCT. There were 36 infants classified as LTFU, 52.8% (19/36) had at most 1 consult after discharge translating to a missed opportunity for virological testing. Overall LTFU rate was at 33.3% (95% CI 25.7% to 42.7%). In our setting, financial constraints and hospital proximity were some of the problems encountered. Thailand became the first Asian country to achieve WHO's target for the elimination of MTCT. In a study by Thisyakorn, MTCT rate was reduced from 20-40% to 1.9% in 2015 due to a pragmatic multi-sector response. Key factors that contributed to MTCT elimination were: an effective monthly monitoring system to improve missed opportunities for prevention; primary prevention of HIV in women of childbearing age through family planning programs, counseling and voluntary HIV testing; prevention of unintended pregnancies in women living with HIV by recommending dual methods of contraception for HIV-infected women and their partners; prevention of HIV transmission from a woman living with HIV to her infant by receiving free WHO Option B + through the national PMTCT programme; and provision of appropriate treatment, care and support to women and children living with HIV through HIV testing, CD4 testing and clinical staging to determine eligibility for ART in both pregnant women and infants.[17]

For better understanding of how the PMTCT evolved in our setting, Figure 4 shows a timeline of our PMTCT program. Changes were based on data from international guidelines. Our PMTCT program was adapted from two major guidelines, WHO[14] and the Aidsinfo U.S. guidelines.[15,18] Therefore, interventions varied among patients. We roughly assessed the protocol uptake and discovered that 91.2% (62/68, excluding 2 HIV infected infants) were given guideline-compliant management. This may have contributed to the low MTCT rate, although adherence studies should be done to support this notion. Reasons identified for non-adherence included: incorrect risk stratification, delayed initiation of prophylaxis beyond 12 hours and lack of maternal ART prior to delivery.

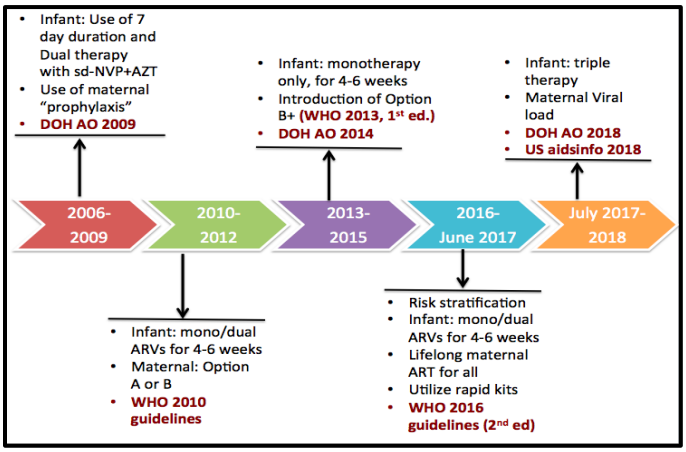

Figure 4. Evolution of PMTCT program in PGH

The PMTCT program is comprised of several components that must be approached comprehensively. Upon reviewing several PMTCT studies done globally,[4,8,9,11,19-25] the following program components have been implicated in vertical transmission of HIV: timely antenatal visit, HIV diagnosis and maternal ART initiation prior to delivery, CD4 count of >200 prior to delivery, life-long triple ART, delivery via cesarean section, infant prophylaxis initiated within 12 hours of life and lasting >4weeks and replacement feeding.

Early antenatal visit translates to an early opportunity for HIV testing resulting in early diagnosis and timely initiation of ART. PMTCT studies in Nigeria and Vietnam found that mothers who enrolled late into

the program had higher odds of transmission due to late initiation of ART.[11,19] Aziz et al. reported that pregnant women with ≥50% adherence, whether ARV-naive or -experienced, achieve a viral load of <1000 copies/ml within a median of 14 days of upon ART initiation.[20] In our institution, mothers are encouraged to undergo HIV screening at the earliest opportunity. Once diagnosed, they are enrolled into care and treatment is immediately started after obtaining baseline diagnostics.

The percentage of HIV positive pregnant women in the Philippines who have access to ART increased from 13% in 2010 to 18% in 2018.[1] In 2010-2013, the WHO recommended Option A and B as maternal prophylaxis. In option A, the regimen will depend on the stage of pregnancy: Antepartum: AZT as early as 14 weeks of pregnancy; Intrapartum: AZT and 3TC plus single dose NVP (sD-NVP) and Postpartum: AZT and 3TC for seven days. In option B, triple ARTs are prescribed but duration will depend on the mother's status. Mothers with CD4 count ≤500 cells/mm^3 or diagnosed with HIV clinical stage 3 or 4 at the time of ART initiation are eligible for lifelong therapy; otherwise, ARTs are discontinued after delivery unless the mother chooses to breastfeed.[26,27] Option B+ was introduced in the 2013 WHO guidelines wherein lifelong ART with TDF + 3TC + EFV were recommended for all HIV positive pregnant and breastfeeding women regardless of clinical stage or CD4 count.[27] Our local guidelines adapted this in 2014.[13] Out of 70 mothers in this study, only 1 (1.4%) was advised Option A, the rest were on Option B (18/70) or B+ (51/70) lifelong regimens. According to Muyunda et al., mothers on Option B+ had 50% reduced risk for MTCT compared to option A or B.[21] Having incorporated this intervention in our program probably contributed to better HIV prevention.

CD4 cells are destroyed by HIV infection, and a lower number correlates with increasing risk of morbidity and mortality. In analyses done in Ethiopia, South Africa, and Uganda, they reported that mothers with CD4 count <200 are at increased risk of transmitting HIV to their infants.[10,12,22] In our study, 85.2% had CD4 counts >200, postulating that this result may have a causal effect on transmission reduction.

Elective cesarean delivery is recommended at 38 weeks of gestation for all HIV-infected pregnant women with HIV RNA levels >1000 copies/mL near the time of delivery (or who have unknown viral load), regardless of the type of maternal ART being received.[18] In our program, 71.4% of mothers have no viral load determination, therefore majority of them delivered via cesarean section. In a study by Warszawski et al., elective cesarean section was inversely associated with MTCT but there was no significant difference in transmission risk among those with viral load of <400 copies/ml.[23] In contrast, a study by Mark et al. found that mode of delivery was not associated with MTCT.[24]

Newborn ARV regimens should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery.[18,28] Initiation of post exposure prophylaxis after 2 days of age is not likely to be efficacious in preventing transmission.[28] Our study showed that 96.8% (60/62) were given prophylaxis within 12 hours suggesting timely drug intervention as a factor in preventing MTCT but additional evaluation found no significant association. The reason for delayed initiation for the 2 patients was not written in the chart. One patient received prophylaxis on the 14th HOL, one on the 18th HOL, both though were not HIV infected.

According to WHO, HIV infected mothers should exclusively breastfeed for the first 6 months of life and may continue breastfeeding while being fully supported for ART adherence.[29] However, they also noted that an additional 5-20% of infants might become infected postnatally during breastfeeding without PMTCT interventions. In situations where breastfeeding cannot be avoided, extended infant prophylaxis would help reduce the risk of transmission.[30] Hence, upon entry into care, mothers are referred to our division for counseling on the choice of infant feeding. In our program, 88.6% opted to give replacement feeding, 2.9% decided to exclusively breastfeed for 6 months and 8.6% initially decided to breastfeed but switched to formula feeding within 6 months. Among those who were exclusively breastfed, prophylaxis was extended to ≥12 weeks. Several studies stated that exposure to breast milk had a higher MTCT rate than replacement feeding.[4,8,9] But other research suggested that breastfeeding was protective against MTCT.[31-33] Studies showed that mixed feeding is a significant determinant of transmission.[25,34] In our study, type of infant feeding was not significantly associated with HIV transmission. Similarly, a study in South Africa found out that morbidity and mortality were similar among HIV-exposed breast-fed and formula-fed infants.[35] These maternal and infant interventions, though not significant on statistical analyses when they were individually analyzed may have collectively

contributed to the low MTCT rate in this study. Additional studies are recommended to support this assumption.

Univariate regression analysis showed that mothers with hepatitis B are 33 times more likely to transmit HIV to their infants. One explanation could be: active co-infection stimulates the release of cytokines and inflammatory agents that enhance HIV replication systemically and weakens natural defenses to MTCT.[36] Persistent viremia and presence of co-infections in infants/mothers may further increase the load leading to immune activation resulting in immune dysregulation that exacerbate disease progression in a positive feedback loop.[37] While there are more studies tackling the reverse effect,[38-40] there were very few researches that investigated the effect on HIV MTCT.[36,41] A study done in India found out that maternal HIV-HBV coinfection did not increase HIV transmission.[41] In our study, 4.3% (3/70) had maternal co-infection with Hepatitis B. 1 out of 3 infants was HIV infected. After statistical analysis, it showed that Hepatitis B was a significant risk factor for MTCT of HIV. The reason for the discordant result remains to be elucidated. To date, this is one of the first researches to suggest this association. Constrained by the small sample size, further studies are needed to verify this information.

The impact of the PMTCT program could be measured in terms of lives saved or infections prevented. In our local registry,[2] a total of 26 deaths were recorded among those who acquired HIV through MTCT since 1984. Out of 117 mother-infant pairs included in the program during the study period, 3 infants expired, 2 out of 3 died within 7 to 10 days, hence, no virological test was done and thus, these infants were excluded. One out of three was HIV infected. The overall mortality rate was 1.4% (1/70) and 50% (1/2) for HIV infected infants. Again, due to the rate of LTFU, this number may be an underestimate. Assuming all LTFU infants expired, worst-case scenario mortality rate would be 36% (39/108). Mortalities in the program were included in the Survival Analysis. All were guideline compliant, delivered term via cesarean section, on replacement feeding, their mothers all had advanced disease (Clinical stage 3 and 4), no viral load testing and on combination lifelong ART (Option B and B+). Differences were seen in the choice of prophylaxis (single, dual, triple regimen) and infant survival was analyzed based on this. Survival rate across these regimens were not significantly different. Haile-Salassie et al. mentioned in a study, that because of selective use of triple prophylaxis for infants at higher risk, it is not appropriate to explore the association of type of prophylaxis and infection status.[42] Moreover, more than 4 weeks of prophylaxis was associated with a significantly higher survival proportion. This was an expected finding since recent guidelines[14,18,43] all recommend a minimum of 6 weeks duration for high-risk infants. This finding supports that the recommended duration is probably effective.

The greatest strength of this study is that it was conducted in the real world setting in one of the tertiary hospitals that caters to majority of HIV exposed infants. As a result, findings are more likely to reflect actual outcomes of PMTCT interventions in urban areas of the Philippines. Unlike other studies, we were able to look into the association of maternal co-infections like Hepatitis B with vertical transmission stressing the importance of antenatal screening and early initiation of maternal ART.

This is the first study in the Philippines to assess the outcomes of a PMTCT program. Our institutional program was well implemented with an uptake of 91.2%. The HIV MTCT rate was 2.86% upon application of our program, meeting the <5% goal of WHO. The rate was lower as compared to theoretical rates (15-45%) without PMTCT interventions. In conclusion, our local PMTCT program is a valuable health intervention strategy that can address the rising number of HIV cases in the Philippines and may be beneficial to other health facilities if adapted. Despite study limitations, in the absence of studies conducted in the Philippines to assess risk factors and effectiveness of PMTCT programs, our findings provide baseline and essential information on possible determinants of HIV transmission that can help improve prevention strategies for both the infant and mother.

RECOMMENDATIONS

This study has several limitations, which will be discussed with proposed recommendations for improvement. First, being a retrospective review, this study was dependent on medical charts with problems on data completeness. Because of this, adherence to medications and feeding practices were not assessed. Prospective studies may be able to control for these confounding variables. Second, we encountered a high rate of LTFU. Hence, the effectiveness of the program

may be overestimated. We recommend an integrated community approach and a unified record system for better inter-hub coordination, which can facilitate infant tracking, support and treatment uptake. It is also important to reinforce our vaccination program, which can increase the follow up rate of our patients. Third, because a number of infants were LTFU, the power of the study was limited due to the small sample size. Hence, we recommend a multicenter study among hospitals providing PMTCT measures. Lastly; maternal viral load determination prior to delivery was not routinely done.[44] We recommend baseline viral load testing to determine the mode of delivery, maternal response to ART and infant risk stratification.

REFERENCES

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Data 2019;137-150,194-195.
2. National HIV/AIDS & STI Surveillance and Strategic Information Unit (NHSSS). DOH HIV/AIDS & ART Registry of the Philippines (HARP) Report. January-March 2020;1-8.
3. World Health Organization. PMTCT Strategic Vision 2010–2015: Preventing mother-to-child transmission of HIV to reach the UNGASS and Millennium Development Goals. Geneva, Switzerland; 2010.
4. Lussiana C, Clemente SVL, Ghelardi A, Lonardi M, Tarquino IAP, Floridia M. Effectiveness of a Prevention of Mother-to-Child HIV Transmission Programme in an Urban Hospital in Angola. PLoS One. 2012;7(4):e36381. doi:10.1371/journal.pone.0036381
5. Ruton H, Mugwaneza P, Shema N, Lyambabaje A, Bizimana JD, Tsague L, et al. HIV-free survival among 9- to 24-month-old children born to HIV-positive mothers in the Rwandan national PMTCT programme: a community-based household survey. J Int AIDS Soc. 2012;15(4):1-11.
6. Nduati, EW, Hassan AS, Knight MG, Muema DM, Jahangir MN, Mwaringa SL, et al. Outcomes of prevention of mother to child transmission of the human immunodeficiency virus-1 in rural Kenya—a cohort study. BMC Public Health. 2015;15(1008):1-12.
7. Noubiap J, Bongoe A, Demanou S. Mother-to-child transmission of HIV: Findings from an Early Infant Diagnosis program in Bertoua, Eastern Cameroon. Pan African Medical Journal. 2013; 15:65.
8. Agboghoroma CO, Audu LI, Iregbu KC. Effectiveness of prevention of mother-to-child transmission of HIV program in Abuja, Nigeria. Journal of HIV & Human Reproduction. Jan-June 2015; 3(1): 7-13.
9. Mwendo EM, Mtuy TB, Renju J et al. Effectiveness of prevention of mother-to-child HIV transmission programmes in Kilimanjaro region, northern Tanzania. Tropical Medicine and International Health. 2014;19(3):267–274.
10. Akinsanya OS, Wiseberg-Firtell JA, Akpomiemie G, Adeniyi OV, Kaswa RP. Evaluation of the prevention of mother-to-child transmission programme at a primary health care centre in South Africa. S Afr Fam Pract. 2017;52(5):56–60.
11. Nguyen TTV, Sabin K, Ho TQT, Le AKA, Chika H, Kato M. Monitoring Prevention Impact of Mother-to-Child Transmission of HIV in Concentrated Epidemics With Program and Survey Data. JMIR Public Health Surveill. 2017;3(4):e76.
12. Birlie B, Diriba TA, Sisay K, Gurmessa A, Seyoum D, Tadesse M. Mother to Child HIV Transmission and Its Predictors among HIV-Exposed Infants: A Retrospective Follow-Up Study in Southwest Ethiopia. J AIDS Clin Res. 2016;7(9):1-7.
13. Department of Health Administrative Order 2014-0031. Policies and Guidelines on the Use of Antiretroviral Therapy (ART) Among People Living with Human Immunodeficiency Virus (HIV) and HIV-Exposed Infants. 2014;1-19.
14. World Health Organization. Consolidated Guidelines On The Use Of Antiretroviral Drugs For Treating And Preventing HIV Infection Recommendations For A Public Health Approach, 2nd ed. Geneva, Switzerland; 2016.
15. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (USA). Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 2017 November [accessed 2018 July 31]. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf
16. Nyandiko WM, Otieno-Nyunya B, Musick B, Bucher-Yiannoutsos S, Akhaabi P, Lane K, et al. Outcomes of HIV-Exposed Children in Western Kenya: Efficacy of Prevention of Mother to Child Transmission in a Resource-Constrained Setting. J Acquir Immune Defic Syndr. 2010;54:42-50.
17. Thisyakorn, U. Elimination of mother-to-child transmission of HIV: lessons learned from success in Thailand. Paediatrics and International Child Health. 2017;37(2):99-108.
18. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (USA). Recommendations for Use of ARV Drugs in Pregnant HIV-1 infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. 2018 April [accessed 2018 July 31]. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf
19. Sowale OY, Olakunde BO, Obi C, Itiola AJ, Erhunmwunse Y, Melvin SC. Risk factors for perinatal transmission of HIV among women attending prevention of mother-to-child transmission clinics in Northwest Nigeria. AIDS Care. 2019; 31(3):326-332.
20. Aziz N, Sokoloff A, Kornak J, Neva NV, Mendiola ML, Levison J, et al. Time to viral load suppression in antiretroviral-naive and -experienced HIV-infected pregnant women on highly active antiretroviral therapy: Implications for pregnant women presenting late in gestation. British Journal of Obstetrics and Gynaecology. 2013;120 (20):1534-1547.
21. Muyunda B, Musonda P, Mee P, Todd J, Michelo C. Effectiveness of Lifelong ART (Option B+) in the Prevention of Mother-to-Child Transmission of HIV Programme in Zambia: Observations Based on Routinely Collected Health Data. Front. Public Health. Jan 2020;7:401.
22. Izudi J, Apangu P, Bajunirwe F, Mulogo E, Batwala V.High Baseline CD4 Count and Exclusive Breastfeeding Are Associated with Lower Rates of Mother to Child HIV

Transmission in Northwestern Uganda: A Two-Year Retrospective Cohort Study. Advances in Public Health. 2018; Article ID 4140254:1-8.
23. Warszawski J, Tubiana R, Chenadec JL, Blancheg S, Teglasa JP, Dollfusi C, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. AIDS. 2008;22:289-299.
24. Mark S, Murphy KE, Reads S, Bitnun A, Yudin MH, et al. HIV Mother-to-Child Transmission, Mode of Delivery, and Duration of Rupture of Membranes: Experience in the Current Era. Infectious Diseases in Obstetrics and Gynecology. 2012;Article ID 267969:1-5.
25. Li B, Zhao Q, Zhang X, Wu L, Chen T, Liang Z, et al. Effectiveness of a prevention of mother-to-child HIV transmission program in Guangdong province from 2007 to 2010. BMC Public Health. 2013;13:591.
26. World Health Organization HIV/AIDS Programme. Antiretroviral Drugs For Treating Pregnant Women And Preventing HIV Infection In Infants: Recommendations for a Public Health Approach. 2010;20-54.
27. World Health Organization. Consolidated Guidelines On The Use Of Antiretroviral Drugs For Treating And Preventing HIV Infection Recommendations For A Public Health Approach, First Edition, 2013; 59-72, 91-130.
28. Havens PL, Mofenson LM, AAP Committee on Pediatric AIDS. Evaluation and Management of the Infant Exposed to HIV-1 in the United States. PEDIATRICS. January 2009;123(1):175-187.
29. WHO United Nations Children's Fund. Guideline: updates on HIV and infant feeding: the duration of breastfeeding, and support from health services to improve feeding practices among mothers living with HIV. 2016;12-32.
30. Kumwenda NI, Hoover DR, Mofenson LM, Thigpen MC, Kafulafula G, Li Q, et al. Extended Antiretroviral Prophylaxis to Reduce Breast-Milk HIV-1 Transmission. N Engl J Med. 2008;359:119-129.
31. Gueye SB, Diop-Ndiaye H, Diouf O, Sow-Ndoye A, Toure F, Ngom-Faye NF, et al. Effectiveness of the prevention of mother-to-child transmission program (PMTCT) via Early Infant Diagnosis (EID) data in Senegal. PLoS ONE. 2019;14(5): e0215941.
32. Flynn PM, Taha TE, Cababasay M, Fowler MG, Mofenson LM, Owor M, et al. Prevention of HIV-1 transmission through breastfeeding: Efficacy and safety of maternal antiretroviral therapy versus infant nevirapine prophylaxis for duration of breastfeeding in HIV-1-infected women with high CD4 cell count (IMPAACT PROMISE): a randomized, open label, clinical trial. Acquir Immune Defic Syndr. 2018;77(4):383–392.
33. Ngwende S, Gombe NT, Midzi S, Tshimanga M, Shambira G, Chadambuka A. Factors associated with HIV Infection Among Children Born to Mothers on the Prevention of Mother to Child Transmission Programme at Chitungwiza Hospital, Zimbabwe, 2008. BMC Public Health. 2013;13:1181.
34. Endalamaw A, Demsie A, Eshetie S, Habtewold TD. A systematic review and meta-analysis of vertical transmission route of HIV in Ethiopia. BMC Infectious Diseases. 2018;18:283.
35. Rollins NC, Becquet R, Bland RM, Coutsoudis A, Coovadia HM, Newell M. Infant Feeding, HIV transmission and Mortality at 18 months: The need for appropriate choices by mothers and prioritization within programmes. AIDS. 2008;22(17):2349-2357.
36. King CC, Ellington SR, Kourtis AP. The Role of Co-Infections in Mother-to-Child Transmission of HIV. Curr HIV Res. 2013;11(1):10–23.
37. Muenchhoff M, Prendergast AJ, Goulder PJR. Immunity to HIV in early life. Frontiers in Immunology. 2014;5(391):1-13.
38. Andersson MI, Maponga TG, Ijaz S, Theron G, Preiser W, Tedder RS. High HBV Viral Loads in HIV-Infected Pregnant Women at a Tertiary Hospital, South Africa. J Acquir Immune Defic Syndr. 2012;60(4):e111-e112.
39. Chasela CS, Kourtis AP, Wall P, Drobeniuc J, King CC, Thai H, et al.Hepatitis B virus infection among HIV-infected pregnant women in Malawi and transmission to infants. J Hepatol. 2014;60(3):508–514.
40. Chotuna N, Nel E, Cotton MF, Preiser W, Andersson MI. Hepatitis B virus infection in HIV-exposed infants in the Western Cape, South Africa. Vaccine. 2015;33:4618–4622.
41. Mave V, Kadam D, Kinikar A, Gupte N, Bhattacharya D, Bharadwaj R, et al. Impact of Maternal Hepatitis B Virus Coinfection on Mother-to-Child Transmission of Human Immunodeficiency Virus. HIV Med. 2014;15(6):347–354.
42. Haile-Selassie HT, Townsend CL, Tookey PA. Use of neonatal post-exposure prophylaxis for prevention of mother-to-child HIV transmission in the UK and Ireland, 2001–2008. HIV Medicine. 2011;12:422–427.
43. Department of Health Administrative Order 2018-0024: Revised Policies and Guidelines on the use of Antiretroviral Therapy (ART) among People Living with HIV and HIV-exposed Infants. 2018;1-27.
44. Philippine Obstetrical and Gynecological Society: Clinical Practice Recommendations on Prevention of Mother to Child Transmission of HIV Infection (PMTCT) 2015;1-26.