HEALTH SCIENCES AND DISEASES
The Journal of Medicine and Health Sciences

Original Article

Programmatic Challenges in Implementing PMTCT Option B+ and Pediatric HIV Care: Baseline Assessment from *"Save the Families for Africa"* in Malawi

Les défis programmatiques dans l'implémentation de la PMTE Option B+ et de la prise en charge du VIH pédiatrique: une évaluation préliminaire au Malawi

Joseph Fokam[1,2,3]*, Maria Mercedes Santoro[1], Isabel Chimbiri[4], Jeremoni Chindiura[4], Ruth Deula[4], Alex Rombe[4], Riccardo Massari[4], Agness Lungu[4], Carlo-Federico Perno[1,2,5]

1. Faculty of Medicine and Surgery, University of Rome "Tor Vergata", Rome, Italy;
2. Chantal BIYA International Reference Centre for research on HIV/AIDS prevention and management, Yaoundé, Cameroon;
3. Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon;
4. Likuni Mission Hospital, Likuni, Malawi;
5. AVARALIA Foundation, Rome, Italy.

***Corresponding author**:
Dr. Joseph Fokam, PhD. Infect Dis
Email:
josephfokam@gmail.com,
fokamjoseph@circb.cm

Keywords: HIV; eMTCT; infant feeding option; early infant diagnosis; pediatric care.

ABSTRACT

Objective. With high rates of HIV-infection among pregnant women living in sub-Saharan Africa (SSA), risks of mother-to-child transmission (MTCT) remain concerning in spite of current progress. Thus, identifying gaps in the era of option-B+ would generate specific evidence-based interventions. **Methods.** A baseline assessment for "*SAVE THE FAMILIES FOR AFRICA*" project, a retrospective study was conducted throughout 2014 at the Likuni Mission Hospital in Malawi based on performance indicators of the prevention of MTCT (PMTCT) cascade and pediatric antiretroviral therapy (ART) care. **Results.** In 2014, 7.5% (199/2658) newborns were vertically exposed to HIV and all HIV-infected mothers (199) received PMTCT intervention. A rate of 40.8% and 55.1% HIV-infected pregnant/breastfeeding mothers were lost to follow-up at six and 12 months, respectively. Amongst infants (6 [IQR: 6-8] weeks) tested for HIV-1 early infant diagnosis (EID), 79.0% (166/210) EID results were withdrawn, with a median turn-around time (TAT) of 36 [IQR: 30-60] days. 82.5% mothers were on lifelong ART 4 weeks before delivery. Infants received cotrimoxazole (100.0%), nevirapine prophylaxis (91.2%) and exclusive breastfeeding (90.8%). HIV-1 MTCT was 2.8% (6/215), with higher age (p=0.07) and longer TAT (p=0.367) among infected-infants. For pediatric ART, dispensing practices and drug supply were excellent (100%), while on-time drug pick-up (69.7%) and retention in care (70.9%) were poor. **Conclusions.** Progress in option-B+ and pediatric ART care are encouraging in this SSA setting, but may be hampered by lost to follow-up and poor adherence. Eliminating MTCT and sustaining pediatric ART performance in SSA require a holistic interventional approach for universal access to healthcare.

RÉSUMÉ

Objectif. La forte prévalence du VIH chez les femmes enceintes en Afrique sub-Saharienne (SSA) suggère un risque considérable de la transmission mère-enfant (TME) malgré progrès enregistrés. Dans cette optique, identifier les goulots d'étranglement dans l'ère option-B+ permettrait la mise en œuvre des interventions probantes. **Méthodes.** Une étude retrospective a été menée dans le cadre du projet "*SAVE THE FAMILIES FOR AFRICA*" durant l'année 2014 à l'Hôpital Missionnaire de Likuni au Malawi, sur la base de la performance des indicateurs de la cascade en prévention de la TME (PTME) et prise en charge du VIH pédiatrique (ART). **Résultats**. Durant cette année, 7,5% (199/2658) de nouveaux nés avaient subi une exposition verticale au HIV et toutes les femmes enceintes infectées par le VIH (199) étaient enrôlées dans la PTME MTCT. Un taux de 40,8% et 55,1% des femmes enceintes/allaitantes était perdue de vue à six et à 12 mois après enrôlement. Parmi les enfants (6 [IQR: 6-8] d'âge semaines) testés pour le diagnostic précoce du VIH (EID), 79,0% (166/210) des résultats étaient retirés, dans une délai de 36 [IQR: 30-60] jours. 82.5% des mères étaient sous trithérapie antirétrovirale (TARV) 4 au moins 4 semaines avant l'accouchement. La prophylaxie au cotrimoxazole était de 100,0% chez les enfants, prophylaxie à la nevirapine de 91,2% et l'allaitement maternel and exclusif de 90,8%. le taux de TME était de 2,8% (6/215), légèrement élevé avec l'âge avancé (p=0,07) et le temps de retrait de résultats (p=0,367). Concernant la TARV pédiatrique, les practices de dispensation et la délivrance des médicaments étaient excellentes (100%), les taux de retrait des médicaments dans les délais (69,7%) et de rétention (70,9%) étaient faibles. **Conclusions**. L'option-B+ s'accompagne d'excellents progrès en PTME et prise en charge pédiatrique du VIH au Malawi. Une optimisation des performances nécessite des interventions visant à limiter les perdues de vue et les cas d'inobservance, a travers une approche holistique autour du couple mère-enfant.

INTRODUCTION

HIV among pregnant women in sub-Saharan Africa

Sub-Saharan Africa (SSA) is still facing high burdens of HIV-infection that disproportionately affects women, with higher incidence in the key population of pregnant women (WHO, 2014a; UNAIDS, 2014). Among pregnant women, HIV prevalence ranges from 7.8% in Cameroon (Billong *et al.,* 2015) to 31.7% in South Africa (Woldesenbet *et al.,* 2015), favored by sustained horizontal transmission (WHO, 2014b). In the Malawian context (10.3 % HIV prevalence), 59% of infected individuals are women (UNAIDS, 2014), with consequently 68,000 vertical exposures for 16.2% infant infections yearly (UNAIDS, 2013a). Thus, closing existing gaps would help in an effective elimination of MTCT (eMTCT).

PMTCT programs in sub-Saharan Africa

PMTCT interventions entail a cascade of services: antenatal care (ANC) attendance; HIV testing and counselling; antiretroviral provision for all seropositive pregnant/breastfeeding women; safe delivery and infant prophylaxis; safer infant feeding practices; early infant diagnosis (EID); postnatal family planning and mother-child follow-up; HIV rapid-testing (at 12 and 24 months); discharge after month-24 or linking HIV-positive infants/children to care (UNAIDS, 2013a; WHO, 2014c). Interventions have evolved from single-dose nevirapine, option-A, option-B, to option-B+ (lifelong antiretroviral therapy [ART] for HIV-infected pregnant/breastfeeding women, regardless of CD4 count or clinical stage) in several SSA PMTCT high priority countries (WHO, 2013; Edmonds *et al.,* 2015).

Implementation of PMTCT option-B+

By June 2014, about 50% and 100% respectively of the World Health Organization (WHO) HIV focus and Global Plan priority countries have endorsed option-B or B+ (WHO, 2014b). As national programs are transitioning to option-B+, reaching all HIV-infected mothers is key in reducing MTCT to <5% (or even fewer) in breastfeeding and down to <2% in non-breastfeeding populations (Tubiana *et al.,* 2010; UNICEF and BLC, 2012; WHO, 2013).

In SSA, option-B+ was first implemented in Malawi in July 2011; followed by 12 other countries as of end 2014 (UNICEF and BLC, 2012; WHO Afro, 2014; Government of Malawi, 2015). In spite of significant benefits recorded with option-B+ in Malawi, MTCT remains non-negligible nationwide, hence underscoring the need to identify programmatic gaps (Kim *et al.,* 2015). As a pioneer in option-B+, the Malawi experience would address state-of-the-art for eliminating MTCT (eMTCT) in several resource-limited settings (RLS).

HIV-1 Early infant diagnosis and pediatric care

A key component of the PMTCT cascade, early infant diagnosis (EID) aims at identifying HIV-1-infected infants for timely ART initiation (UNAIDS, 2013b; Mwendo *et al.,* 2014; Saounde Temgoua *et al.,* 2015). Inopportunely, EID is performed in less than half of HIV-exposed infants, which partly justifies the low pediatric ART coverage (WHO, 2014b). As consequence, pediatric ART program (23%, range 21–25%) lags behind that of adults (37%, range 35–39%), underscoring the need of further investigations/interventions, especially in SSA where 90% of the 3.2 million HIV-infected children are living (WHO, 2014a). Evidence-based interventions are therefore needed for universal access to ART (UNAIDS, 2013b).

Gaps in PMTCT option-B+ and pediatric care

eMTCT has several bottle nets, starting from incomplete ANC coverage in RLS (27%–95%), gaps between ANC attendance and delivery in a health facility (4%–45%) and maternal mortality (Berhan *et al.,* 2014). Secondly, poorly integrated ANC/HIV service and community-based interventions affect uptake in option-B+ (Herlihy *et al.,* 2015). Furthermore, the outcome of some mother-child remains unknown within the PMTCT cascade (Rawizza *et al.,* 2015), especially in rural or remote areas (Escamilla *et al*., 2015; Edmonds *et al.,* 2015).

Study Objectives

As a baseline assessment for "*SAVE THE FAMILIES FOR AFRICA*" project, we sought to ascertain the rate of HIV-vertical exposure, the effectiveness of PMTCT and pediatric ART care, in a typical RLS in Malawi.

METHODS

Study design

Using a retrospectively design, an assessment was conducted on the effectiveness of PMTCT option-B+ and pediatric HIV care at the Likuni Mission Hospital (LMH) in Malawi.

Site description

LMH is a health facility located 9 km west of Lilongwe (capital of Malawi), with 231 beds capacity for a catchment area of 168,904 inhabitants (mainly low-income farmers, small-scale traders, and sub-urban wage earners) and accessible to an estimate of 978,700 city residents; offering eleven community-health outreach clinics with expanded reach of health services to remote areas (http://www.likunimissionhospital.org/about-us/who-we-are/). With 3,750 expected annual deliveries, ANC and PMTCT services are integrated; ART clinic is operational since 2005, with 5814 patients enrolled on ART by end-December 2014.

Based on its geographical context, its socio-economical situation and experience in option-B+, LMH represents a suitable SSA setting to identify gaps in the era of B+ and generate evidence-based interventions for uptake and global eMTCT.

Data collection on PMTCT care cascade

The study-reporting period was January through December 2014. Maternal data were abstracted from ANC registers of 2014 (containing information on ANC attendance; maternal acceptance for HIV testing; maternal HIV results). This observational period was selected was chosen because the service interventions was implemented from 2015 through the SFA programme.

Data on HIV-exposed infants/children were abstracted from the EID *MasterCards* of 2014 (containing

information on maternal ART; infant nevirapine and cotrimoxazole prophylaxes; practice of formula, mixed or breastfeeding; EID result; EID turn-around-time ([TAT]). Briefly, HIV-vertically exposed infants were tested for EID at 6 weeks of age or at the earliest visit thereafter; EID was based on polymerase chain reaction of the Roche Amplicor® HIV-1 DNA test kit version 1.5 using dried blood spots (DBS) from cards, as previously described (Dube *et al.*, 2012).

Data abstraction for HIV paediatric care

Data abstracted from the database (*ART version 2.0 beta*) in 2014 was used to evaluate the performance of pediatric ART care following programmatic and clinic indicators throughout the year 2014 as per the updated WHO HIV drug resistance (HIVDR) early warning indicator (EWI) tools, from EWI_1 to EWI_5 defined as follows (WHO, 2012):

1) ***EWI_1 (On-time pill pickup)****: Percentage of ART children whose prescribed ARV drugs are all picked up on time;*

2) ***EWI_2 (Retention in care)****: Percentage of children known to be alive and on treatment after initiation of ART;*

3) ***EWI_3 (No drug stock-outs)****: Percentage of months without ARV drug stock-outs;*

4) ***EWI_4 (Dispensing practices)****: Percentage of pediatric patients picking up ART without mono or dual ARV therapy;*

5) ***EWI_5 (Virological suppression)****: Percentage of pediatric patients receiving ART at the site after the first 12 months of ART and whose viral load is less than 1000 copies/ml.*

Statistical analysis

An Excel spreadsheet version 2010 was used for data entry and analysis of PMTCT-cascade indicators, while the WHO routine data quality assessment (RDQA) tool was used to analyse the EWIs of pediatric ART monitoring.

Percentage or proportions were calculated as numerator over denominator; factors associated with risks of MTCT and children follow-up were analysed using Fisher's exact test, with p-value <0.05 considered statistically significant.

Survival rates among pregnant and breastfeeding mothers receiving lifelong ART (option B+) at 6 and 12 months of follow-up, as well as survivals of HIV-1-infected children receiving paediatric combination ART were evaluated by using both ART registers and the official Malawian ART database *(ART version 2.0 beta*).

HIV-exposed/infected children and HIV-infected mothers who did not return to clinic 90 days after the last scheduled appointment were considered lost to follow-up.

Ethics considerations

The study was part of the activities implemented by the LMH and the *AVIRALIA* foundation, to support PMTCT uptake. Following the retrospective design, informed consent was not required as data were retrieved from source documents, and de-identified for purpose of confidentiality.

RESULTS

Maternal profile within the PMTCT program in 2014

Acceptance for HIV testing was 100%. A total of 288 ANC attendees were declared seropositive for HIV, of whom 199 delivered in 2014 at LMH.

The number of deliveries per quarter increased overtime (from 531 to 732), similarly to the number of HIV-related deliveries (from 39 to 57), as detailed in Fig.1.

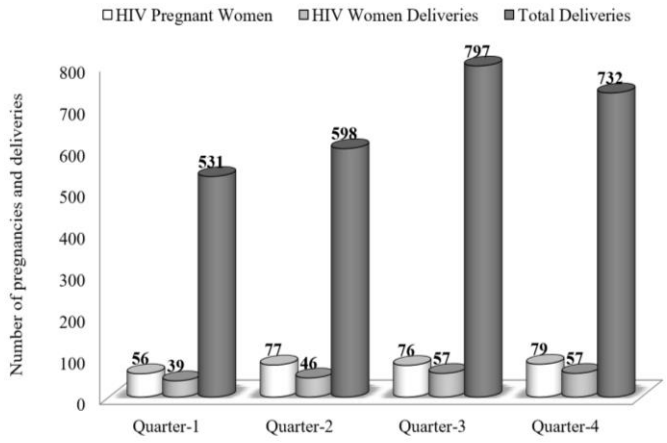

Figure 1. Number of pregnancies and deliveries occurring quarterly in 2014.

Legend: HIV: human immunodeficiency virus.

The annual rate of HIV-vertically exposed infants was 7.5% (199 out of 2658 babies delivered in Likuni Mission Hospital), with closely similar quarterly trends: from 7.3% (39/531) in the first Quarter (January-March), 7.7% (46/598) in the second quarter (April-June), 7.2% (57/797) in the third quarter (July-September), to 7.8% (57/732) in the fourth quarter (October-December) (Fig. 1).

Maternal PMTCT interventions in 2014

All HIV-infected pregnant women received lifelong ART. Of those with available details, 82.1% (160/195) were on ART before pregnancy and 12.8% (25/195) received late PMTCT interventions (less than four weeks ART or at the onset of labor, due to late HIV diagnosis during pregnancy), as reported in Fig.2.

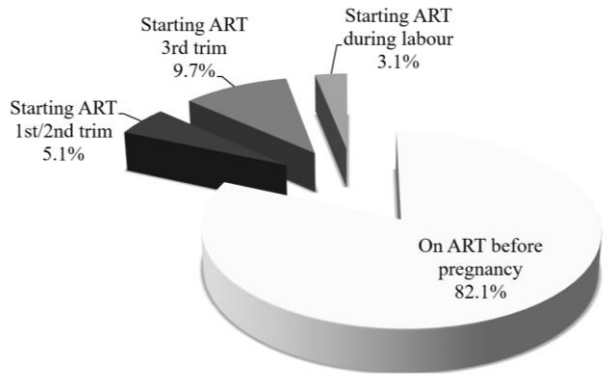

Figure 2. Maternal PMTCT interventions in 2014 at the Likuni Mission Hospital (LMH).

Legend: ART: antiretroviral therapy; LMH: Likuni Mission Hospital; PMTCT: Prevention of Mother-to-Child Transmission of HIV.

Survival rates among HIV-infected mothers enrolled in 2014

Among 78 pregnant and breastfeeding women newly enrolled on lifelong ART (option B+) in 2014, outcomes at 6 and 12 months revealed high rates of lost to follow-up (40.8% and 55.1%, respectively), and only one case of death was reported (Table 1).

Table 1. Survival analysis of mothers enrolled in 2014

Performance indicators	6-months N (%)	12-months N (%)
Newly enrolled on PMTCT Option B+	71 (100%)	78 (100%)
Alive and on PMTCT Option B+	34 (59.2%)	34 (43.6%)
Died after enrollment	0 (0%)	1 (1.3%)
Lost to follow-up from the cohort	**29 (40.8%)**	**43 (55.1%)**

Legend: PMTCT: prevention of mother to child transmission

Performance of HIV-1 early infant diagnosis in 2014 profile of HIV-vertically exposed children

In total, 217 infants (median age: 6 [IQR: 6-8] weeks, min-max: 1-40) were tested for HIV-1 EID throughout 2014. Of them, five were transferred and two did not have EID result available. Among the remaining 210 infants, for 166 (79.0%) EID results were delivered to the mother/caregiver, while 44 were lost to follow-up including two cases of EID HIV-1-positive infants.

The median TAT, from DBS sampling to EID result delivered to mother/caregiver, was 36 days [IQR: 30-60], min-max (20-197); resulting to ≥one-quarter mothers/caregivers withdrawing EID results 2 months after DBS-phlebotomy.

For infant prophylaxis, all (100%) received cotrimozaxole prophylaxis against opportunistic infections, 91.2% received 6-weeks postnatal nevirapine versus 3.2% without any prophylaxis. For infant feeding option, 90.8% were on exclusive breastfeeding while 3.7% had a mixed feeding, indicating risks of HIV acquisition throughout the course of breastfeeding occurring after the first HIV testing around 6 weeks of age. Regarding maternal ART, 82.5% were receiving lifelong ART (i.e. option B+) for more than four weeks before delivery, versus 8.8% late ART initiation, 3.2% without any ART, and 1.4% AZT monotherapy (Table 2).

Table 2. Clinical profile of HIV-vertically exposed children

Infant prophylaxis	**6 weeks NVP**	**NVP only at birth**	**None**	**Unknown prophylaxis**	
Percentage (n)	91.2% (198)	1.9% (4)	3.2% (7)	3.7% (8)	
Infant feeding option	**Exclusive breastfeeding**	**Mixed Feeding**	**Formula Feeding**	**Unknown Feeding**	
Percentage (n)	90.8% (197)	3.7% (8)	3.2% (7)	2.3% (5)	
Maternal PMTCT	**Option B+ (>4 weeks)**	**Option B+ (0-3 weeks)**	**AZT Monotherapy**	**None**	**Unknown PMTCT**
Percentage (n)	82.5% (198)	8.8% (19)	1.4% (3)	3.2% (7)	4.1% (9)

Legend: Option B+ indicates lifelong triple antiretroviral therapy; AZT: Zidovudine; n: number; NVP: Nevirapine; PMTCT: prevention of mother-to-child transmission.

For clinical outcomes, all infants were reported asymptomatic except one (suspected tuberculosis later not confirmed); while for the nutritional profile showed all infants were reported without malnutrition, even during the known hunger annual season (around August-November).

HIV-1 MTCT and related features

The rate of HIV-1 MTCT was 2.79% (6/215) for infants tested and with available DNA-PCR results in 2014. Among these HIV-1-positive infants, 50% of mother-child pairs received interventions with PMTCT option B+ (maternal ART and infant NVP). Moreover, HIV-1-positive infants had a higher median age at EID testing (16 weeks) compared to those uninfected (six weeks, p=0.07) as well as a longer TAT (38.5 days) compared to those uninfected (36 days, p=0.367) (Table 3). This further suggests that for children tested "only early (i.e. around 6 weeks of age)" might have gotten infection later if breastfed.

Table 3. Basic characteristics of HIV-vertically infected infants

Median [IQR] age at EID testing, weeks	16 [13; 20]
EID Result withdrawal, % (n/N)	66.7% (4/6)
Median [IQR] Turn-Around-Time (TAT), days	38.5 [23; 41]
PMTCT history of mother-child pair, % (n/N)	
Maternal ART (>4 weeks) plus infant NVP	33.3% (2/6)
Maternal ART (0-3 weeks) plus infant NVP	16.7% (1/6)
….Maternal ART (>4 weeks), no infant NVP	
Mother-child without any intervention	16.7% (1/6)
Mother-child with unknown PMTCT exposure	16.7% (1/6)
	16.7% (1/6)

Legend: EID: Early Infant Diagnosis, IQR: Interquartile range; NVP: Nevirapine, PMTCT: Prevention of Mother-To-Child-Transmission.

Outline of ART program and pediatric care in 2014

Throughout the year 2014, 683 people initiated ART, of whom 34.4% (235) pregnant/breastfeeding women and 6.3% (43) children, with only 1.8% (12) aged <2 years old.

Indicators of Pediatric HIV care and monitoring

Out of the five indicators (EWI) used to monitoring children enrolled on ART in 2014 (WHO, 2012), EWI_5 was not feasible due to inaccessibility to viral load measurement (Table 4).

Table 4. Indicators of pediatric ART throughout 2014

	Definition	Targets	Performance	Interpretation
EWI_1	*Percentage of ART children whose prescribed ARV drugs are all picked up on time in 2014*	Desirable (≥95%) Fair (85-95%) Poor (<85%)	69.7% (23/32)	Poor performance
EWI_2	*Percentage of children known to be alive and on treatment after initiation of ART in 2014*	Desirable (>85%) Fair (75–85%) Poor (<75%)	70.9% (12/17)	Poor performance
EWI_3	*Percentage of months without ARV drug stock-outs in 2014*	Desirable (100%) Poor (<100%)	100% (12/12)	Desirable performance
EWI_4	*Percentage of pediatric patients picking up ART without mono or dual ARV therapy*	Desirable (100%) Poor (<100%)	100% (32/32)	Desirable performance
EWI_5	*Percentage of pediatric patients receiving ART at the site after the first 12 months of ART whose viral load < 1000 copies/ml*	Desirable (>85%) Fair (70–85%) Poor (<70%)	Not available (inaccessibility to viral load locally)	Not applicable

Legend: ARV: antiretroviral; ART: antiretroviral therapy;

Out of the four evaluated EWIs, two achieved the desirable performance of 100%: EWI_3 (no monthly pediatric ARV stock-outs) and EWI_4 (good dispensing practices of pediatric triple ART). The two other indicators EWI_1 (on-time drug pick-up) and EWI_2 (retention in care) indicated a poor performance (EWI_1: 69.7%; EWI_2: 70.9%) among those achieving 12 months follow-up (by end-May 2015) after initiation.

Survival analysis of children on ART in 2014

Among children on ART in 2014, 35% (14/40) were lost to follow-up after 12 months of ART initiation, with semester rates increasing from 25% to 45% (Table 5).

Table 5. Outcomes of children newly enrolled on ART with 12 months follow-up in 2014

	Quarter-1 (N=12)	Quarter-2 (N=8)	Quarter-3 (N=14)	Quarter-4 (N=6)	Total 2014 (N=40)
Alive and on ART	7 (8.4%)	6 (75%)	8 (57.1%)	3 (50%)	24 (60%)
Died	1 (8.3%)	0 (0%)	0 (0%)	0 (0%)	1 (2.5%)
Lost to follow-up	**3 (25%)**	**2 (25%)**	**6 (42.9%)**	**3 (50%)**	**14 (35%)**
Stopped ART	1 (8.3%)	0 (0%)	0 (0%)	0 (0%)	1 (2.5%)

Legend: In bold are lost to follow-up as major challenge in the pediatric ART program.

Further assessment of survival analysis among children achieving 24 months monitoring in 2014 (Table 6) revealed an increased lost to follow-up (46.7%) as compared to those at 12 months monitoring (35%), p=0.25.

Table 6. Outcomes of children newly enrolled on ART with 24 months follow-up in 2014

	Quarter-1 (N=24)	Quarter-2 (N=10)	Quarter-3 (N=15)	Quarter-4 (N=11)	Total 2014 (N=60)
Alive and on ART	12 (50%)	03 (30%)	08 (53.3%)	05 (45.4%)	28 (46.7%)
Died	00 (0%)	01 (10%)	0 (0%)	0 (0%)	1 (1.6%)
Lost to follow-up	**10 (41.7%)**	**05 (50%)**	**07 (46.7%)**	**06 (54.6%)**	**28 (46.7%)**
Transfer out on ART	2 (8.3%)	1 (10%)	0 (0%)	0 (0%)	3 (5%)

Legend: In bold are lost to follow-up as major challenge in the pediatric ART program.

DISCUSSION

The present study is an appraisal of PMTCT performance and the quality of paediatric HIV care, in order to generate baseline findings for specific interventions.

The high acceptance of HIV testing during ANC is encouraging, and was due to counseling on the benefits of PMTCT (Billong *et al.*, 2015; Tenthani *et al.*, 2015). Increasing access to ANC would scaled-up PMTCT coverage (Ladner *et al.*, 2015). The 2,658 reported deliveries, out of 3,750 expected (~29.1% gap), suggest inaccessibility to ANC and ongoing risks of HIV-vertical transmission (WHO Afro, 2014; Woldersenbert *et al.*, 2015). Since home deliveries have greater risk of infecting the child, wider ANC coverage is needed in the community.

The lifelong ART, largely provided to HIV infected pregnant and breastfeeding mothers, confirms option B+ implementation in Malawi (WHO Afro, 2014; Herce *et al.*, 2015). However, efforts to limit late ART initiation (i.e. ~13%) are needed for PMTCT (Tenthani *et al.*, 2015), including fully integrated ANC/PMTCT services (UNICEF, 2009; Billong *et al.*, 2015; Herlihy *et al.*, 2015).

The increasing rate of mothers lost to follow-up underscores the relevance of continuous adherence counseling throughout PMTCT-cascade-care (Tweya *et al.*, 2014), especially for those with higher CD4 (Giuliano *et al.*, 2015), living in distant communities (Horwood *et al.*, 2015), or experiencing local barriers to adequate healthcare (Uwimana *et al.*, 2012; Tilahun *et al.*, 2015; Osoti *et al.*, 2015).

Low rate of maternal mortality, in the frame of lifelong ART, suggests greater health benefits while scaling-up option B+ and limiting defaulters from PMTCT-cascade (Tweya *et al.*, 2014; Kim *et al.*, 2015).

Regarding EID, about 75% were PCR-tested at the recommended age (6 weeks), indicating good practices at LMH. However, with 31% EID results not picked-up, counseling mothers/caregivers on the relevance of infant HIV status would improve best PMTCT practices locally (McCollum *et al.*, 2012).

Low rate of MTCT (<5%) indicates effectiveness of PMTCT-interventions: option B+ (91.3%), infant nevirapine (91.2%), and exclusive breastfeeding (90.8%), as earlier reported (Mwendo *et al*, 2014; Saounde Temgoua *et al.*, 2015; Kim *et al.*, 2015).

Children were all reported asymptomatic, likely due to the protective effect of cotrimozaxole against opportunistic infections (Revill *et al.*, 2015) and the absence of children reported with malnutrition (Chitete *et al.*, 2015).

As half of HIV-1-positive infants received effective PMTCT-interventions (maternal ART and infant NVP), further investigations would help in mitigating risks of MTCT with adherence-levels, virological response and emerging drug resistance (Rawizza *et al.*, 2015; Wadonda-Kabondo *et al.*, 2012; Palombi *et al.*, 2015).

The higher age at EID testing and a longer TAT, reported among HIV-1-infected infants, suggest poor adherence, supported by the high rate of defaulters from the PMTCT cascade-care (Kim *et al.*, 2015; Tejiokem *et al.*, 2015).

Regarding pediatric ART care, ARV dispensing practices were adequate to recommended guidelines (likely favored by fixed dose combinations). No ARV stock out indicates a functional drug supply mechanism. However, delayed pill pick-up and poor retention on ART represented major early warning indicators of HIVDR emergence, thus supporting adherence counseling to mitigate lost to follow-up (Billong *et al.*, 2012; Billong *et al.*, 2013; Bigna et al., 2014; Fokam *et al.*, 2015; Woldesenbet *et al.*, 2015).

Assessing the role of viral load as an indicator was not feasible. However, implementing viral load testing is crucial for effective monitoring of ART response (Fokam *et al.*, 2011) and PMTCT interventions in such RLS, using a holistic intervention (Teerawattananon *et al.*, 2014).

CONCLUSION

Despite considerable HIV vertical exposure in this Malawian context, MTCT appears below the target of 5%. However, the high rate of lost to follow up, the low rate or lack of testing after breastfeeding, etc, limit the breath of observations. Thus, in an era of option B+, continuous PMTCT interventions are required to limit the rate of defaulters/lost to follow-up. Though pediatric ART program is highly operational (standard regimens and constant drug availability), there are needs to implement viral load testing for HIVDR prevention.

FUNDING

This study was financially supported by the Fondazione Silvana Paolini Angelucci ONLUS (http://www.fondazionesilvanapaolini.it/), and the Italian Foundation for Antiviral Studies and Research (AVIRALIA, http://www.aviraliafoundation.org/).

ACKNOWLEDGEMENTS

We are very grateful to staff of the LMH, especially the team of the antenatal care (ANC) and prevention of mother-to-child transmission (PMTCT) service, the HIV clinic, the pharmacy, the statistics and the administration departments. We thank Amalia Mastrofrancesco for her contribution in the project management.

CONFLICT OF INTEREST

Authors declare there is no potential conflict of interest related to this work.

REFERENCES

1. Berhan Y, Berhan A (2014). Antenatal Care as a Means of Increasing Birth in the Health Facility and Reducing Maternal Mortality: A Systematic Review. *Ethiopian J of Health Sciences* **24**, 93-104.
2. Billong SC, Fokam J, Billong EJ, Nguefack-Tsague G, Essi MJ, Fodjo R, Sosso SM, Gomba A, Mosoko-Jembia J, Loni-Ekali G, Colizzi V, Bissek AC, Monebenimp F, Nfetam JB. [Epidemiological distribution of HIV infection among pregnant women in the ten regions of Cameroon and strategic implications for prevention programs]. Pan Afr Med J. 2015: 20:79. doi: 10.11604/pamj.2015.20.79.4216. eCollection 2015.
3. Billong SC, Fokam J, Nkwescheu AS, Kembou E, Milenge P, Tsomo Z, Dion GN, Aghokeng AF, Mpoudi EN, Ndumbe PM, Colizzi V, Elat Nfetam JB. Early warning indicators for HIV drug resistance in Cameroon during the year 2010. PLoS One. 2012;7(5):e36777. doi: 10.1371 / journal .pone .0036777
4. Bigna JJ, Noubiap JJ, Plottel CS, Kouanfack C, Koulla-Shiro S. Factors associated with non-adherence to scheduled medical follow-up appointments among Cameroonian children requiring HIV care: a case-control analysis of the usual-care group in the MORE CARE trial. Infect Dis Poverty. 2014 Dec 3;3(1):44. doi: 10.1186/2049-9957-3-44. eCollection 2014.
5. Chitete L, Puoane T. What Health Service Provider Factors Are Associated with Low Delivery of HIV Testing to Children with Acute Malnutrition in Dowa District of Malawi? PLoS One. 2015 May 1;10(5):e0123021. doi: 10.1371/ journal.pone.0123021. eCollection 2015.
6. Dube Q, Dow A, Chirambo C, Lebov J, Tenthani L, Moore M, Heyderman RS, Van Rie A; CHIDEV study team. Implementing early infant diagnosis of HIV infection at the primary care level: experiences and challenges in Malawi. Bull World Health Organ. 2012 Sep 1;90(9):699-704.
7. Edmonds A, Feinstein L, Okitolonda V, Thompson D, Kawende B, Behets F. Decentralization does not assure optimal delivery of PMTCT and HIV-exposed infant services in a low prevalence setting. J Acquir Immune Defic Syndr. 2015 Aug 17.
8. Escamilla V, Chibwesha CJ, Gartland M, Chintu N, Mubiana-Mbewe M, Musokotwane K, Musonda P, Miller WC, A Stringer JS, Chi BH. Distance from household to clinic and its association with the uptake of prevention of mother-to-child HIV transmission regimens in rural Zambia. J Acquir Immune Defic Syndr. 2015 Jun 26.
9. Fokam J, Salpini R, Santoro MM, Cento V, Perno CF, Colizzi V, Ndumbe PM, Fokunang Ntungen C, Ndiang Tetang SM, Nanfack AJ, Takou Komego DA, Cappelli G. Drug resistance among drug-naive and first-line antiretroviral treatment-failing children in Cameroon. Pediatr Infect Dis J. 2011 Dec;30(12):1062-8. doi: 10.1097/INF.0b013e31822db54c.
10. Fokam J, Elat JB, Billong SC, Kembou E, Nkwescheu AS, Obam NM, Essiane A, Torimiro JN, Ekanmian GK, Ndjolo A, Shiro KS, Bissek AC. Monitoring HIV Drug Resistance Early Warning Indicators in Cameroon: A Study Following the Revised World Health Organization Recommendations. PLoS One. 2015 Jun 17;10(6):e0129210. doi: 10.1371/journal.pone.0129210.
11. Giuliano M, Liotta G, Andreotti M, Mancinelli S, Buonomo E, Scarcella P, Amici R, Jere H, Sagno JB, Di Gregorio M, Marazzi MC, Vella S, Palombi L. Retention, transfer out and loss to follow-up 2 years after delivery in a cohort of HIV+ pregnant women in Malawi. Int J STD AIDS. 2015 May 6. pii: 0956462415585450.
12. Government of Malawi. Malawi AIDS Response Progress Report 2015. April 2015. http://www.unaids.org/sites/default/files/country/documents/MWI_narrative_report_2015.pdf
13. Herce ME, Mtande T, Chimbwandira F, Mofolo I, Chingondole CK, Rosenberg NE, Lancaster KE, Kamanga E, Chinkonde J, Kumwenda W,Tegha G, Hosseinipour MC, Hoffman IF, Martinson FE, Stein E, van der Horst CM.

Supporting Option B+ scale up and strengthening th e prevention of mother-to-child transmission cascade in central Malawi: results from a serial cross-sectional study. BMC Infect Dis. 2015 Aug 12; 15:328. doi: 10.1186/s12879-015-1065-y.

14. Herlihy JM, Hamomba L, Bonawitz R, Goggin CE, Sambambi K, Mwale J, Musonda V, Musokatwane K, Hopkins KL, Semrau K, Hammond EE, Duncan J, Knapp AB, Thea DM. Integration of PMTCT and antenatal services improves combination antiretroviral therapy cART uptake for HIV-positive pregnant women in Southern Zambia - A prototype for Option B+? J Acquir Immune Defic Syndr. 2015 Jul 15.
15. Horwood CM, Youngleson MS, Moses E, Stern AF, Barker PM. Using adapted quality-improvement approaches to strengthen community-based health systems and improve care in high HIV-burden sub-Saharan African countries. AIDS. 2015 Jul; 29 Suppl 2:S155-64. doi: 10.1097/QAD.0000000000000716.
16. Kim MH, Ahmed S, Hosseinipour MC, Yu X, Nguyen C, Chimbwandira F, Paul ME, Kazembe PN, Abrams EJ. Impact of Option B+ on the Infant PMTCT Cascade in Lilongwe, Malawi. J Acquir Immune Defic Syndr 2015;70:99–103
17. Ladner J, Besson MH, Rodrigues M, Saba J, Audureau E. Performance of HIV Prevention of Mother-To-Child Transmission Programs in Sub-Saharan Africa: Longitudinal Assessment of 64 Nevirapine-Based Programs Implemented in 25 Countries, 2000-2011. PLoS One. 2015 Jun 22;10(6):e0130103. doi: 10.1371/journal.pone.0130103. eCollection 2015.
18. McCollum ED, Johnson DC, Chasela CS, Siwande LD, Kazembe PN, Olson D, Hoffman I, van der Horst C, Hosseinipour MC. Superior uptake and outcomes of early infant diagnosis of HIV services at an immunization clinic versus an "under-five" general pediatric clinic in Malawi. J Acquir Immune Defic Syndr. 2012 Aug 1;60(4):e107-10. doi: 10.1097/QAI.0b013e31825aa721.
19. Mwendo EM, Mtuy TB, Renju J, Rutherford GW, Nondi J, Sichalwe AW, Todd J. Effectiveness of prevention of mother-to child HIV transmission programmes in Kilimanjaro region, northern Tanzania. Trop Med Int Health. 2014 Mar;19(3):267-74. doi: 10.1111/tmi.12255. Epub 2014 Jan 6.
20. Osoti AO, John-Stewart G, Kiarie JN, Barbra R, Kinuthia J, Krakowiak D, Farquhar C. Home-based HIV testing for men preferred over clinic-based testing by pregnant women and their male partners, a nested cross-sectional study. BMC Infect Dis. 2015 Jul 30;15:298. doi: 10.1186/s12879-015-1053-2.
21. Palombi L, Galluzzo CM, Andreotti M, Liotta G, Jere H, Sagno JB, Luhanga R, Mancinelli S, Amici R, Marazzi MC, Vella S, Giuliano M. Drug resistance mutations 18 months after discontinuation of nevirapine-based ART for prevention of mother-to-child transmission of HIV in Malawi. J Antimicrob Chemother. 2015 Jun 25. pii: dkv171.
22. Penda CI, Bebey FS, Mangamba DK, et al. Échecs thérapeutiques chez les enfants infectés par le VIH en suivi de routine dans un contexte à ressources limitées au Cameroun. *The Pan African Medical Journal*. 2013;15:80. doi:10.11604/pamj.2013.15.80.2754.
23. Rawizza HE, Chang CA, Chaplin B, Ahmed IA, Meloni ST, Oyebode T, Banigbe B, Sagay AS, Adewole IF, Okonkwo P, Kanki PJ; APIN PEPFAR Team. Loss to Follow-Up within the Prevention of Mother-to-Child Transmission Care Cascade in a Large ART Program in Nigeria. Curr HIV Res. 2015;13(3):201-9.
24. Revill PA, Walker S, Mabugu T, Nathoo KJ, Mugyenyi P, Kekitinwa A, Munderi P, Bwakura-Dangarembizi M, Musiime V, Bakeera-Kitaka S, Nahirya-Ntege P, Walker AS, Sculpher MJ, Gibb DM. Opportunities for improving the efficiency of paediatric HIV treatment programmes. AIDS. 2015 Jan 14;29(2):201-10. doi: 10.1097/QAD.0000000000000518.
25. Saounde Temgoua EM, Nkenfou CN, Zoung-Kanyi Bissek AC, Fokam J, Billong SC, Sosso SM, Tangipumdu C, Elong EL, Domkan I, Colizzi V.
26. HIV-1 Early Infant Diagnosis is an Effective Indicator of the Prevention of Mother-to-Child Transmission Program Performance: Experience from Cameroon. Curr HIV Res. 2015;13(4):286-91.
27. Teerawattananon Y, Tantivess S, Werayingyong P, Kingkaew P, Tin N, Aye SS, Myint P. Evidenceinformed policy formulation: the case of the voucher scheme for maternal and child health in Myanmar. WHO South-East Asia J Public Health. 2014;3(3-4): 285–288.
28. Tejiokem MC, Warszawski J, Ndongo FA, Ndiang ST, Ndongo JA, Owona F, Ngoupo PA, Tchendjou P, Kfutwah A, Penda IC, Faye A. Feasibility of Routinely Offering Early Combined Antiretroviral Therapy to HIV-Infected Infants in a Resource-Limited Country: The ANRS-Pediacam Study in Cameroon. Pediatr Infect Dis J. 2015 Jun 26.
29. Tenthani L, Haas AD, Egger M, Oosterhout JJ, Jahn A, Chimbwandira F, Tal K, Myer L, Estill J, Keiser O. J. Brief Report: HIV Testing Among Pregnant Women Who Attend Antenatal Care in Malawi. Acquir Immune Defic Syndr. 2015 Aug 15;69(5):610-4. doi: 10.1097/QAI.0000000000000669.
30. Tilahun M, Mohamed S. Male Partners' Involvement in the Prevention of Mother-to-Child Transmission of HIV and Associated Factors in Arba Minch Town and Arba Minch Zuria Woreda, Southern Ethiopia. Biomed Res Int. 2015; 2015:763876. doi: 10.1155/2015/763876.
31. Tomlinson M, Doherty T, Ijumba P, Jackson D, Lawn J, Persson LÅ, Lombard C, Sanders

D, Daviaud E, Nkonki L, Goga A, Rohde S, Sitrin D, Colvin M, Chopra M. Goodstart: a cluster randomised effectiveness trial of an integrated, community-based package for maternal and newborn care, with prevention of mother-to-child transmission of HIV in a South African township. Trop Med Int Health. 2014 Mar;19(3):256-66. doi: 10.1111/tmi.12257.

32. Tubiana R, Le Chenadec J, Rouzioux C, Mandelbrot L, Hamrene K, Dollfus C, Faye A, Delaugerre C, Blanche S, Warszawski J. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). Clin Infect Dis. 2010 Feb 15;50(4):585-96. doi: 10.1086/650005.
33. Tweya H, Gugsa S, Hosseinipour M, Speight C, Ng'ambi W, Bokosi M, Chikonda J, Chauma A, Khomani P, Phoso M, Mtande T, Phiri S. Understanding factors, outcomes and reasons for loss to follow-up among women in Option B+ PMTCT programme in Lilongwe, Malawi. Trop Med Int Health. 2014 Nov;19(11):1360-6. doi: 10.1111/tmi.12369
34. UNAIDS. Global Report: UNAIDS report on the global AIDS epidemic 2013. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2013a. p. 116. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Global_Report_2013_en_1.pdf.
35. UNAIDS. Ambitious treatment targets: Writing the final chapter of the AIDS epidemic. Reference Discussion paper. Geneva: UNAIDS; 2013b.
36. UNAIDS. The Gap Report. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2014. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf.
37. UNICEF. Demographic and Health Surveys, Multiple Indicator Cluster Surveys and other national household surveys: Antenatal care coverage, Figure 3.3. Geneva: UNICEF; 2009. Available from: http://www.unicef.org/sowc09/docs/SOWC09-Figure-3.3-EN.pdf
38. UNICEF and Business Leadership Council. A business case for options B and B+: To eliminate mother-to-child transmission of HIV by 2015. Geneva: UNICEF, 2012. Available from: http://www.unicef.org/aids/files/DISCUSSION_PAPER.A_BUSINESS_CASE_FOR_OPTIONS_B.pdf
39. Uwimana J, Jackson D, Hausler H, Zarowsky C. Health system barriers to implementation of collaborative TB and HIV activities including prevention of mother to child transmission in South Africa. Trop Med Int Health. 2012 May;17(5):658-65. doi: 10.1111/j.1365-3156.2012.02956.x.
40. Wadonda-Kabondo N, Banda R, Moyo K, M'bang'ombe M, Chiwaula M, Porter C, Jordan MR. Prevalence of Transmitted HIV Drug Resistance Among Newly Diagnosed Antiretroviral Therapy–Naive Pregnant Women in Lilongwe and Blantyre, Malawi. Clin Infect Dis. 2012 May 15; 54(Suppl 4): S324–S327. doi: 10.1093/cid/cir993
41. Woldesenbet S, Jackson D, Lombard C, Dinh TH, Puren A, Sherman G, Ramokolo V, Doherty T, Mogashoa M, Bhardwaj S, Chopra M, Shaffer N, Pillay Y, Goga A; South African PMTCT Evaluation (SAPMCTE) Team. Missed Opportunities along the Prevention of Mother-to-Child Transmission Services Cascade in South Africa: Uptake, Determinants, and Attributable Risk (the SAPMTCTE). PLoS One. 2015: 6;10(7):e0132425. doi: 10.1371/journal.pone.0132425. eCollection 2015
42. World Health Organisation. Using early warning indicators to prevent HIV drug resistance Report of the Early Advisory Indicator Panel meeting (11-12 August 2011). ISBN: 978 92 4 150394 5. Geneva: World Health Organisation; 2012 [cited 2015 Jun 15]. Available from: http://www.who.int/hiv/pub/meetingreports/ewi_meeting_report/en/
43. World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. Geneva: World Health Organisation; 2013 [cited 2015 Jun 15]. Available from: http://www.who.int/hiv/pub/guidelines/arv2013/en/
44. World Health Organisation. Global summary of the HIV/AIDS epidemic. Geneva: World Health Organisation; 2014a [cited 2015 Jun 15]. Available from: http://www.who.int/hiv/data/epi_core_dec2014.png?ua=1.
45. World Health Organization. HIV/AIDS: Global update on the health sector response to HIV, 2014. World Health Organization; 2014b [cited 2015 Jun 15]. ISBN: 978 92 4 150758 5. Available from: http://www.who.int/hiv/pub/progressreports/update2014/en/
46. World Health Organization. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Geneva: World Health Organisation; 2014c [cited 2015 Jun 15]. ISBN 978 92 4 150743 1.
47. World Health Organisation Regional Office for Africa. Implementation of Option B+ for Prevention of Mother-To-Child Transmission of HIV: The Malawi Experience. Republic of Congo; 2014. Available from: http://www.zero-hiv.org/wp-content/uploads/2014/04/Implementation-of-Option-B+-for-prevention-of-mother-to-child-transmission-of-hiv.pdf