

ORIGINAL RESEARCH

The National Evaluation of Malawi's PMTCT Program (NEMAPP) study: 24-month HIV-exposed infant outcomes from a prospective cohort study

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Abstract

Objectives: Data on long-term HIV-free survival in breastfeeding, HIV-exposed infants (HEIs) are limited. The National Evaluation of Malawi's Prevention of Mother-to-Child Transmission (PMTCT) Program (NEMAPP), conducted between 2014 and 2018, evaluated mother-to-child transmission (MTCT) and infant outcomes up to 24 months postpartum.

Methods: We enrolled a nationally representative cohort of HEIs at 54 health facilities across four regional strata in Malawi and used multivariable Cox regression analysis to investigate the risk of adverse outcomes (HIV transmission, infant death and loss to follow-up) to 24 months postpartum. Models, controlling for survey design, were fitted for the total cohort ($n = 3462$) and for a subcohort that received maternal viral load (VL) monitoring ($n = 1282$).

Results: By 24 months, in 3462 HEIs, weighted cumulative MTCT was 4.9% [95% confidence interval (CI) 3.7–6.4%], 1.3% (95% CI 0.8–2.2%) of HEIs had died, 26.2% (95% CI 24.0–28.6%) had been lost to follow-up and 67.5% (95% CI 65.0–70.0%) were alive and HIV-free. Primiparity [weighted adjusted hazard ratio (aHR) 1.6; 95% CI 1.1–2.2; parity 2–3: weighted aHR 1.5; 95% CI 1.2–1.9], the mother not disclosing her HIV status to her partner (no disclosure: weighted aHR 1.3; 95% CI 1.1–1.6; no partner: weighted aHR 0.7; 95% CI 0.5–0.9), unknown maternal ART start (weighted aHR 2.0; 95% CI 1.0–3.9) and poor adherence (missed ≥ 2 days of ART in the last month: weighted aHR 1.7; 95% CI 1.2–2.2; not on ART: weighted aHR 1.7; 95% CI 1.0–2.7) were associated with adverse outcomes by 24 months. In the subcohort analysis, risk of HIV transmission or infant death was higher among HEIs whose mothers started ART post-conception (during pregnancy: weighted aHR 3.2; 95% CI 1.3–7.7; postpartum: weighted aHR 12.4; 95% CI 1.5–99.6) or when maternal viral load

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at enrolment was > 1000 HIV-1 RNA copies/mL (weighted aHR 15.7; 95% CI 7.8–31.3).

Conclusions: Infant positivity and infant mortality at 24 months were low for a breastfeeding population. Starting ART pre-conception had the greatest impact on HIV-free survival in HEIs. Further population-level reduction in MTCT may require additional intervention during breastfeeding for women new to PMTCT programmes. Pre-partum diagnosis and linkage to ART, followed by continuous engagement in care during breastfeeding can further reduce MTCT but are challenging to implement.

KEYWORDS

disclosure, HIV-exposed infants, HIV-free survival, Malawi, mother–infant pairs, Option B+, prevention of mother-to-child transmission, treat all

INTRODUCTION

In 2011, the Malawi Ministry of Health streamlined their prevention of mother-to-child transmission (PMTCT) programme by pioneering ‘Option B+’, a universal test-and-treat strategy for HIV-infected pregnant and breastfeeding women, resulting in dramatic increases in the uptake of antiretroviral treatment (ART) among HIV-infected women [1]. Currently, estimates of HIV testing and ART coverage among HIV-infected pregnant women at antenatal clinics comfortably surpass 90% [2,3]. Following the adoption of ‘Option B+’ by the World Health Organization in 2012, almost all sub-Saharan countries have transitioned to this strategy [4]. However, limited national- and population-level data are available describing the impact of universal ART coverage on reducing mother-to-child transmission (MTCT) during pregnancy, delivery and breastfeeding, mainly because of ongoing programmatic challenges with uptake of early infant diagnosis (EID) and long-term follow-up [2,5].

Malawi is among the first African countries to report national estimates of early MTCT (measured at < 12 weeks of delivery) under Option B+. The National Evaluation of Malawi’s PMTCT Program (NEMAPP) study, conducted between 2014 and 2018, measured early MTCT as 3.7% [95% confidence interval (CI) 2.3–6.0%] [6], representing a substantial decline from an earlier population-based estimate of 8.5% (95% CI 6.6–10.7%) in the first few months of Option B+ [7]. Similarly, in Zimbabwe, national estimates have shown a reduction in early MTCT from 6.6% to 2.0% following Option B+ implementation [8]. In Zimbabwe, cumulative 18-month MTCT dropped from 7.0% to 3.3% after introduction of Option B+ [8,9]. The proportion of MTCT occurring after 12 weeks postpartum before and after implementation of Option B+ was 44.0% and 39.4%, respectively [8,9]. This is consistent with South African

estimates during the transition from Option A to B, showing that 39.5% of MTCT happened between 12 weeks and 18 months postpartum [10].

Although there are positive national-level results regarding prevention of early infant HIV transmission, limited data exist on long-term effectiveness throughout the duration of breastfeeding. Here we present 24-month outcomes of MTCT and HIV-free survival in a nationally representative prospective cohort of HEIs in the NEMAPP study.

METHODS

Study design

The NEMAPP methods are described in detail elsewhere [2,6]. NEMAPP used a multistage cluster design to recruit a nationally representative cohort of 1–6-month-old HEIs and their mothers. The sampling frame included all 579 health facilities that provided PMTCT services in Malawi in 2012–2013. We estimated that enrolment of at least 3376 HEIs was required to determine the ratio of MTCT at 24 months postpartum reliably. Probability-proportional-to-size sampling, without replacement, was used to select 54 study facilities across four regional strata. We included a subcohort of 1324 HIV-positive mothers to estimate viral load (VL) suppression. This subset was derived by using probability-proportional-to-size sampling methods to select 13 sites across the eight districts from the original 54 sites, the sample size of which was based on an estimated 50% suppression rate and 50% loss to follow-up for a precision of 2.5% with a 95% CI and an assumed design effect of 2.0.

Between October 2014 and May 2016, all mother–infant pairs (MIPs) attending an under-five clinic or

other out-patient clinic in the 54 study facilities were consecutively invited for interview and screening for HIV. Separate consent was provided for screening for HIV and for inclusion in the study if mothers were HIV positive. Eligibility criteria for the MIPs included confirmed HIV exposure in infants, infant age between 1 and 6 months at the time of screening, and mother present at the screening or confirmed dead by a legal guardian. Infants with caregivers whose mothers were alive but not present were not eligible.

We screened 33 980 MIPs for HIV, including 236 (0.7%) guardians of infants whose mothers were confirmed dead. HIV exposure was confirmed in 3566 of the 33 980 MIPs (10.5%). Of those, mothers of 3462 HEIs (3383 singletons, 38 twins and one triplet) consented and were enrolled for longitudinal follow-up.

Data collection and laboratory procedures

MIPs were followed up at 12 and 24 months postpartum, with observed window periods of 10–18 and 20–28 months postpartum, respectively. At enrolment and at 12 and 24 months, mothers (or guardians) were interviewed by trained health facility staff using structured questionnaires to obtain sociodemographic information, HIV status at screening, disclosure to partner status, uptake and timing of PMTCT/ART, self-reported health status and adherence to treatment (as self-reported number of days of missed ART in the last month), uptake of infant nevirapine (NVP) prophylaxis from birth, early infant diagnosis (EID) after 6 weeks of age, uptake of infant cotrimoxazole preventive treatment (CPT) and breastfeeding. When possible, mothers' health booklets and Ministry of Health registers were checked for accuracy of responses.

A positive rapid test (Determine[®] [Alere, Tel Aviv, Israel] as the first test and Unigold[®] [Trinity Biotech, Bray, Ireland] for confirmation) and positive antibody test by means of an enzyme immunoassay (EIA) (Murex HIV-1.2.0; DiaSorin, Dartford, UK) in the mother and/or infant indicated infant HIV exposure. A qualitative HIV-1 DNA polymerase chain reaction (PCR) test (COBAS AmpliPrep/COBAS TaqMan Qualitative assay version 2.0; Roche Diagnostics, Indianapolis, IN, USA) was performed on all HEI samples to determine whether the infant was HIV infected at enrolment. At infant age 12- and 24-month follow-up visits, rapid testing and PCR were repeated to determine whether the infant was infected during the breastfeeding period. Rapid test results were provided immediately to the mother as per Malawi's national HIV testing guidelines, and PCR results were provided during the next routine clinic visit.

Maternal HIV viral load (VL) testing was conducted on venous samples (Abbott Real-Time HIV-1 Assay; Abbott Laboratories, Chicago, IL, USA) from all women in the subcohort, regardless of ART status, at enrolment and at 12 and 24 months postpartum. VL suppression was defined as HIV-1 RNA < 1000 copies/mL as per the Malawi national HIV guidelines [11].

Statistical analyses

We report infant outcomes, and maternal and infant characteristics by infant outcome [i.e. HIV-positive (diagnosed either during or after enrolment), died, lost to follow-up or HIV-free at 24 months], as unweighted numbers and weighted categorical proportions with 95% CIs, and used χ^2 tests to determine the significance of differences in characteristics between infants with any adverse outcome (HIV transmission, infant death or lost to follow-up) and those with HIV-free survival.

We used survival analysis to describe the effect of adverse outcomes to 24 months postpartum. The infant outcome age was calculated as the number of months from the infant birth date to the documented outcome date. The loss to follow-up infant outcome by definition includes some deaths and some cases of transmission; therefore, we stratified our analyses based on all known or documented outcomes not including loss to follow-up, and all adverse outcomes including loss to follow-up.

With weighted Cox regression analysis, we calculated weighted unadjusted and adjusted hazard ratios (HRs) for (a) documented adverse outcomes (transmission and death) and (b) all adverse outcomes (loss to follow-up, transmission and death) at 24 months with 95% CIs and *P*-values in two models. In model 1, we fitted maternal age, parity, disclosure to partner status, maternal ART start and mother's adherence to ART at enrolment and uptake of infant NVP and CPT in the total cohort, and in model 2 we added maternal VL at enrolment as a subcohort analysis. We adjusted for all the variables included in both models.

Weighted Kaplan–Meier survival plots were used to present 24-month survival and (a) time to all adverse events, (b) time to all adverse events by category of timing of maternal ART initiation, and (c) time to documented adverse events by category of timing of maternal ART initiation.

Secondary outcomes of the relatively small group of HIV-infected infants are described as unweighted numbers and proportions.

Analyses were conducted using IBM SPSS STATISTICS 26 (IBM, Armonk, NY, USA), and were adjusted for the complex survey design, including sample weight realization

accounting for sampling interval, and probabilities of districts, clusters and subjects being selected.

Ethical approval

Ethical approval for the study was provided by Malawi's National Health Sciences Research Committee (#1262), the Institutional Review Board of the University of Toronto (#30448), and the US Centers for Disease Control and Prevention (CDC) (#2014-057). All participants provided written informed consent.

RESULTS

The numbers of infants enrolled and followed through to 24 months are shown in [Figure 1](#).

Weighted analysis showed that, among the 3462 HEIs, 145 (4.1%; 95% CI 3.1–5.5%) HEIs aged 1–6-months tested HIV positive at the time of enrolment and another 16 (0.8%; 95% CI 0.3–1.9%) tested HIV positive during follow-up. By the 24-month study visit, weighted cumulative MTCT was 4.9% (95% CI 3.7–6.4%), 41 (1.3%; 95% CI 0.8–2.2%) HEIs had died, 1236 (26.2%; 95% CI 24.0–28.6%) had been lost to follow-up and 2024 (67.5%; 95% CI 65.0–70.0%) were alive and HIV-free.

We describe the maternal and infant characteristics by infant outcome [i.e. HIV positive (diagnosed either during

or after enrolment), died, lost to follow-up or HIV-free] in [Table 1](#).

Unweighted median age at infant HIV diagnosis was 2.7 months [interquartile range (IQR) 1.6–3.8 months] during enrolment and 18.4 months (IQR 13.7–23.8 months) post-enrolment. Unweighted median age at infant death and at documented date of being lost to follow-up was 10.6 (IQR 7.1–16.7) months and 13.9 (IQR 10.6–22.9) months, respectively. HIV-free survival was determined at an unweighted median age of 24.2 months (IQR 23.6–25.0 months).

Maternal characteristics

Of the 3462 HEIs, 3245 (94.1%; 95% CI 92.6–95.2%) were born to known HIV-positive mothers, 200 (5.4%; 95% CI 4.3–6.7%) were born to mothers who were newly diagnosed as HIV positive at study enrolment, and for 17 HEIs (0.5%; 95% CI 0.2–1.3%) the biological mother had died.

Mothers' ages ranged from 14 to 51 years; 873 (22.9%; 95% CI 20.7–25.2%) were young mothers (14–24 years). Parity ranged from 1 to 12; 420 (8.9%; 95% CI 7.6–10.5%) were primiparous, 1466 (36.65%; 95% CI 34.1–39.2%) had parity 2–3 and 1571 (54.5%; 95% CI 51.8–57.1%) had parity ≥ 4 . Among the 420 primiparas and 1886 mothers with few children (fewer than four), 338 (83.8%; 95% CI 77.8–88.7%) and 825 (45.3%; 95% CI 41.5–49.2%) were young mothers. Mothers of HEIs with adverse outcomes were

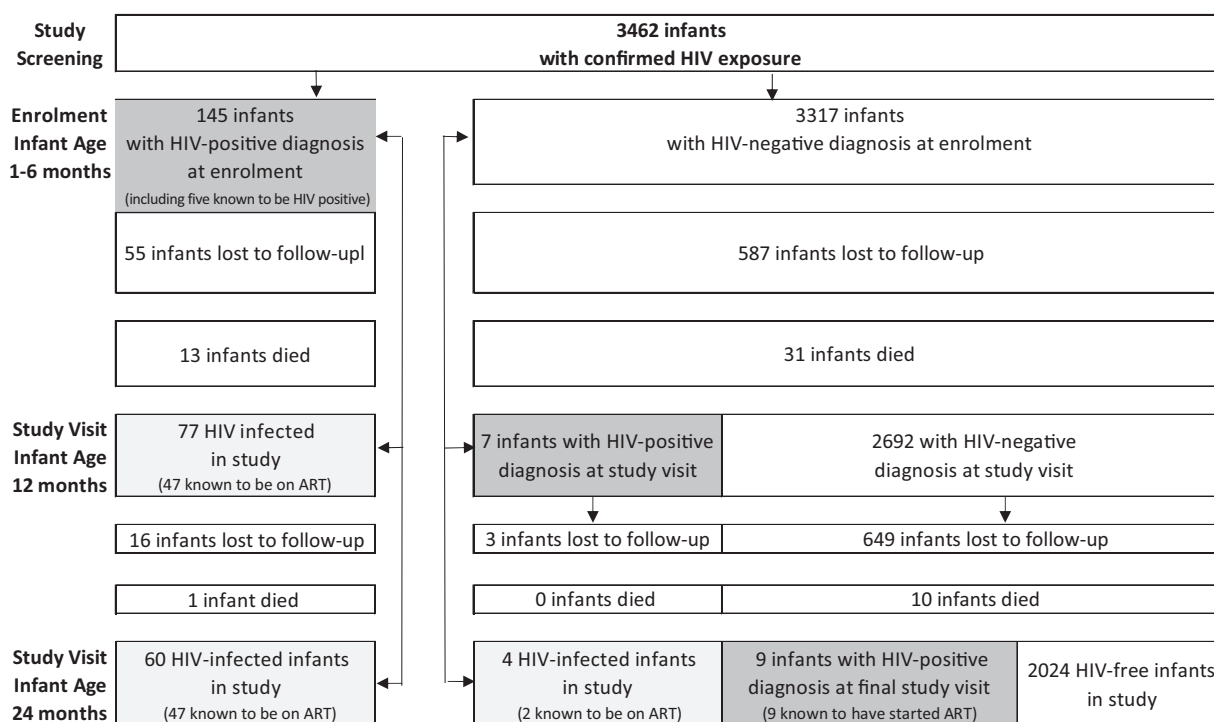


FIGURE 1 Flow chart for HIV-exposed infants enrolled and followed in the study to 24 months

TABLE 1 Maternal and infant characteristics by infant outcome at 24 months

	Adverse Outcomes				
	Documented Adverse Outcomes (n = 201)			Lost to follow-up	HIV-free
	HIV-positive diagnosis at study enrolment Infant age 1-6 months	HIV-positive diagnosis at study visits Infant age 10+ months	Infant Death		
unweighted	n 145	16	41	1236	2024
Infant Age at Infant Outcome, unweighted median months (IQR)	2.7 (1.6-3.8)	18.4 (13.7-23.8)	10.6 (7.1-16.7)	13.9 (10.6-22.9)*	24.2 (23.6-25.0)
MATERNAL CHARACTERISTICS	n weighted % (95%CI)	n weighted % (95%CI)	n weighted % (95%CI)	n weighted % (95%CI)	n weighted % (95%CI)
HIV Status at study enrolment					
Mother known HIV-positive	93 64.3 (50.4-76.1)	15 94.9 (61.9-99.5)	38 94.0 (78.1-98.6)	1153 94.3 (91.5-96.2)	1946 95.8 (94.1-97.0)
Mother newly diagnosed at enrolment	51 35.0 (23.3-48.8)		3 6.0 (1.4-21.9)	79 5.4 (3.5-8.2)	67 3.7 (2.6-5.2)
Infant with caregiver (Mother died; infant confirmed exposed at enrolment)	1 0.7 (0.1-5.2)	1 5.1 (0.5-38.1)	-	4 0.3 (0.1-1.0)	11 0.6 (0.2-1.9)
Maternal Age at enrolment (1-6 months postpartum)					
≤24 (young mothers)	57 32.3 (20.6-46.7)	5 18.2 (3.2-59.9)	8 12.2 (3.4-35.2)	353 28.9 (24.5-33.7)	450 20.2 (17.6-22.9)
>24	88 67.7 (53.3-79.4)	11 81.8 (40.1-96.8)	33 87.8 (64.8-96.6)	878 70.8 (66.0-75.2)	1567 79.6 (76.9-82.1)
Missing				5 0.3 (0.1-0.7)	7 0.2 (0.1-0.5)
Parity					
1	25 9.4 (5.0-17.1)	3 4.3 (0.7-23.6)	2 1.0 (0.2-4.5)	182 12.1 (9.5-15.3)	208 7.8 (6.3-9.8)
2-3	77 58.8 (44.8-71.6)	5 9.6 (2.1-34.4)	16 19.1 (8.9-36.2)	581 43.4 (38.7-48.3)	787 33.2 (30.1-36.3)
≥4	43 31.7 (20.6-45.5)	8 86.1 (58.4-96.5)	22 78.7 (61.0-89.7)	470 44.0 (39.2-48.9)	1028 59.0 (55.6-62.2)
Missing			1 1.3 (0.2-9.7)	3 0.5 (0.1-2.1)	7 0.2 (0.0-0.2)
Disclosure of HIV status to partner					
Mother disclosed HIV status to partner (before or after enrolment)	74 54.4 (40.0-68.1)	12 64.9 (17.0-94.4)	29 62.2 (33.6-84.3)	734 61.4 (56.7-65.9)	1300 60.7 (57.4-64.0)
No disclosure reported	40 23.7 (14.4-36.5)	3 34.5 (5.4-83.0)	3 2.9 (0.8-10.7)	361 26.0 (22.3-30.1)	357 18.1 (15.7-20.8)
No partner	29 20.9 (11.5-34.8)	1 0.6 (0.1-6.6)	9 34.9 (13.4-65.0)	139 12.5 (9.7-16.0)	367 21.1 (18.6-24.1)
Missing	2 0.9 (0.2-4.6)			2 0.1 (0.0-0.4)	
Maternal ART start					
Before pregnancy	26 27.5 (14.8-45.2)	2 33.0 (4.8-82.9)	14 29.9 (12.9-55.2)	521 43.7 (39.0-48.6)	992 50.2 (46.8-53.6)
During pregnancy	43 18.5 (11.4-28.5)	13 64.7 (16.9-94.3)	21 44.7 (22.6-69.1)	555 43.4 (38.7-48.3)	834 37.5 (34.3-40.8)
Post-partum (incl 200 newly diagnosed at study enrolment)	63 42.2 (29.0-56.7)	1 2.2 (0.2-20.6)	3 5.5 (1.2-21.6)	124 10.2 (7.5-13.9)	176 11.0 (8.9-13.5)
Unknown when or if started	13 11.9 (5.1-25.1)	-	3 19.9 (3.8-61.1)	36 2.6 (1.6-4.4)	22 1.4 (0.7-2.9)
Mother's adherence to ART at Enrolment (1-6 month post partum)					
missed 0-1 days of ART in the last month	71 55.4 (41.2-68.8)	13 64.3 (16.7-94.1)	27 52.2 (27.3-76.1)	982 81.2 (77.2-84.6)	1738 87.4 (85.1-89.5)
missed ≥2 days of ART in the last month	14 7.2 (2.9-16.6)	3 35.7 (5.9-83.3)	10 40.7 (17.6-68.8)	145 12.2 (9.3-15.9)	186 7.6 (6.1-9.5)
Not on ART (yet, or stopped)	59 36.6 (24.7-50.5)		4 7.0 (1.9-22.5)	107 6.5 (4.7-9.1)	92 4.7 (3.4-6.3)
Missing	1 0.7 (0.1-5.2)			2 0.1 (0.0-0.4)	8 0.3 (0.1-1.2)
Mother's adherence to ART at Infant Outcome Age**					
Reported optimal adherence only (missed <2 days ART in the last month)	71 55.4 (41.2-68.8)	11 59.8 (15.8-92.2)	24 51.3 (26.8-75.2)	1015 81.6 (77.5-85.1)	1896 93.4 (91.5-94.9)
Reported at least once during study to have missed ≥2 days ART in the last month	14 7.2 (2.9-16.6)	5 40.2 (7.8-84.2)	12 43.0 (19.6-70.0)	133 12.1 (9.2-15.7)	102 5.2 (3.9-6.8)
Not on ART (yet, or stopped)	59 36.6 (24.7-50.5)		5 5.7 (2.0-15.2)	87 6.3 (4.3-9.1)	24 1.4 (0.8-2.5)
Missing	1 0.7 (0.1-5.2)			1 0.1 (0.0-0.5)	2 0.0 (0.0-0.1)
Sub Cohort Viral Load at Enrolment	66	2	8	605	601
<1000 (viral load suppression)	19 27.3 (15.9-42.9)	1 9.5 (0.0-100)	6 73.4 (22.8-96.3)	480 79.6 (75.0-83.6)	527 89.8 (86.6-92.3)
≥1000 (unsuppressed viral load)	47 72.7 (57.1-84.1)	1 90.5 (0.0-100)	2 26.6 (3.7-77.2)	120 19.4 (15.5-24.0)	59 7.8 (5.8-10.6)
Missing				5 1.0 (0.4-2.6)	15 2.3 (1.2-4.6)
Sub Cohort Viral Load at Infant Outcome Age**					
<1000 (viral load suppression)	19 27.3 (15.9-42.9)	1 9.5 (0.0-100)	6 73.4 (22.8-96.3)	494 81.4 (76.8-85.2)	550 92.8 (89.8-95.0)
≥1000 (unsuppressed viral load)	47 72.7 (57.1-84.1)	1 90.5 (0.0-100)	2 26.6 (3.7-77.2)	111 18.6 (14.8-23.2)	51 7.2 (5.0-10.2)
INFANT CHARACTERISTICS					
Received infant nevirapine prophylaxis (42 days or less from birth)					
Yes	81 61.6 (47.7-73.8)	14 64.9 (16.8-94.4)	32 81.0 (58.5-92.8)	1087 87.9 (84.5-90.7)	1880 91.3 (89.1-93.1)
No	64 38.4 (26.2-52.3)	2 35.1 (5.6-83.2)	9 19.0 (7.2-41.5)	149 12.1 (9.3-15.5)	144 8.7 (6.9-10.9)
On Cotrimoxazole Preventative Treatment at Enrolment (1-6 month of age)					
Yes	44 33.5 (20.6-49.4)	7 14.5 (3.7-42.7)	19 49.5 (22.4-71.3)	562 46.1 (41.3-51.0)	947 48.3 (44.9-51.7)
No	95 64.1 (48.5-77.2)	8 70 (16.9-96.4)	20 49.4 (25.6-73.6)	599 48.6 (43.8-53.5)	990 48.3 (44.9-51.7)
Missing	6 2.4 (0.9-6.0)	1 0.8 (0.1-8.2)	2 4.7 (0.9-20.9)	75 5.2 (3.4-8.0)	87 3.4 (2.4-4.7)
On Cotrimoxazole Preventative Treatment at Outcome Age**					
Yes	44 33.5 (20.6-49.4)	15 70.0 (16.9-96.4)	23 54.6 (29.8-77.2)	796 67.0 (62.4-71.3)	1917 95.8 (94.0-97.1)
No	95 64.1 (48.5-77.2)	1 30.0 (3.6-83.1)	16 40.7 (19.5-66.2)	393 29.3 (25.2-33.8)	96 4.0 (2.8-5.8)
Missing	6 2.4 (0.9-6.0)		2 4.7 (0.9-20.9)	47 3.7 (2.1-6.5)	11 0.2 (0.1-0.3)
Breastfeeding at Enrolment (1-6 month of age)					
Yes	139 98.0 (94.6-99.3)	16 100.0 (100-100)	39 97.5 (88.3-99.5)	1198 96.3 (93.8-97.8)	1976 97.4 (95.8-98.4)
No	5 1.3 (0.4-3.7)		2 2.5 (0.5-11.7)	38 3.7 (2.2-6.2)	45 2.5 (1.5-4.1)
Missing	1 0.7 (0.1-5.2)				3 0.1 (0.0-0.3)
Breastfeeding at Outcome Age**					
Yes	139 98.0 (94.6-99.3)	13 67.0 (17.1-95.2)	36 93.5 (81.4-97.9)	1046 81.3 (76.8-85.1)	99 5.1 (3.7-7.0)
No	5 1.3 (0.4-3.7)	2 3.0 (0.4-18.9)	5 6.5 (2.1-18.6)	190 18.7 (14.9-23.2)	1793 91.7 (89.6-93.4)
Missing	1 0.7 (0.1-5.2)	1 30.0 (3.6-83.1)			132 3.2 (2.4-4.3)

* Documented LTF date may be months after having missed a study visit
 **As reported during visit of outcome or last reported

HIV: human immunodeficiency virus
 ART: antiretroviral treatment
 LTF: loss to follow-up

younger ($P = 0.001$) and had lower parity ($P < 0.001$) than those of HEIs who were HIV-free.

Of all mothers, 2149 (60.7%; 95% CI 58.1–63.3%) had disclosed their HIV status to their partner, 764 (20.3%; 95% CI 18.3–22.5%) did not disclose their status at any time during the study, and 545 (19.0%; 95% CI 16.9–21.2%) did not have a partner or their relationship had ended, with

significantly higher proportions of nondisclosure among those with adverse outcomes ($P < 0.001$).

Overall, 1555 (47.1%; 95% CI 44.4–49.9%) mothers had started ART prior to pregnancy, 1466 (38.6%; 95% CI 36.0–41.2%) during pregnancy and 367 (11.9%; 95% CI 10.2–13.9%) postpartum (including those newly diagnosed at enrolment), and for 74 (2.4%; 95% CI 1.6–3.6%)

it is unknown when or if ART was started. Compared to mothers of HEIs with adverse outcomes, significantly more mothers of HIV-free surviving infants started ART prior to pregnancy ($P < 0.001$).

At enrolment, 2831 (83.8%; 95% CI 81.8–85.7%) of all mothers self-reported to have missed 0 or 1 day of ART in the last month, 358 (9.4%; 95% CI 8.0–11.2%) had missed ≥ 2 days of ART and 262 (6.5%; 95% CI 5.3–7.8%) were not on ART. Significantly more mothers of HEIs with adverse events missed ≥ 2 days of ART or were not on ART at enrolment ($P < 0.001$). Similarly, at the time of infant outcome, mothers of HEIs with adverse outcomes were more likely to have missed ART or not be on ART than mothers of HEIs that were HIV-free ($P < 0.001$).

Among the subcohort of 1282 mothers with VL monitoring, 929 (83.8%; 95% CI 81.1–86.2%) had suppressed VL at enrolment. Among the 681 mothers of HEIs with adverse outcomes, 170 (24.8%; 95% CI 20.7–29.3%) had unsuppressed VL at enrolment, compared to 51 (7.8%; 95% CI 5.8–10.6%; $P < 0.001$) of the 601 mothers of HEIs that were HIV-free.

Similarly, at the time of infant outcome, the proportion of mothers with unsuppressed VL was significantly higher among those HEIs with adverse outcomes ($P < 0.001$).

Infant characteristics

Of all HEIs, 3094 (88.9; 95% CI 87.0–90.5%) received NVP from birth to the age of ≤ 6 weeks. However, among the 3245 HEIs born to known HIV-positive mothers, 3054 (93.6%; 95% CI 92.0–94.9%) received NVP from birth to the age of ≤ 6 weeks, with no difference between those with adverse outcomes and those who were HIV-free at 24 months.

Among all HEIs, 1579 (46.8%; 95% CI 44.1–49.6%) were on CPT at enrolment, with no difference between those with adverse outcomes and those who were HIV-free. At outcome age, 2795 (84.9%; 95% CI 82.9–86.8%) were on CPT.

At enrolment, at the age of 1–6 months, 3368 (97.2%; 95% CI 96.2–98.0%) of all HEIs were breastfeeding, with no difference between infants with adverse outcomes and those who were HIV-free at 24 months. Among the 16 HEIs that seroconverted after enrolment, 13 (67.0%; 95% CI 17.1–95.2%) were breastfeeding at the time of HIV diagnosis (median 18.4 months of age; IQR 13.7–23.8 months). Among the 2097 infants retained in the study to 24 months, 167 (8.3%; 95% CI 6.5–10.5%) were still breastfeeding, 1797 (88.3; 95% CI 85.9–90.3%) were not or no longer breastfeeding, and for 133 (3.4%; 95% CI 2.4–4.7%) these data were missing.

The effect of maternal and infant characteristics on adverse outcomes and survival time

Risk of documented adverse outcomes (HIV transmission or infant death) was significantly higher among HEIs whose mothers started ART post-conception (postpartum: weighted aHR 2.5; 95% CI 1.0–6.1; unknown: weighted aHR 5.5; 95% CI 1.9–16.4), HEIs whose mothers had missed ≥ 2 days of ART in the last month (weighted aHR 2.7; 95% CI 1.4–5.0) and HEIs who did not receive NVP (weighted aHR 2.2; 95% CI 1.2–3.9) (Table 2).

Parity (primiparous: weighted aHR 1.6; 95% CI 1.1–2.2; parity 2–3: weighted aHR 1.5; 95% CI 1.2–1.9), the mother's disclosure to partner status (no disclosure: weighted aHR 1.3; 95% CI 1.1–1.6; no partner: weighted aHR 0.7; 95% CI 0.5–0.9), maternal ART start (unknown: weighted aHR 2.0; 95% CI 1.0–3.9) and adherence (missed ≥ 2 days of ART in the last month: weighted aHR 1.7; 95% CI 1.2–2.2; not on ART: weighted aHR 1.7; 95% CI 1.0–2.7) were associated with all adverse outcomes to 24 months.

In the subcohort analysis, risk of HIV transmission or infant death was higher among HEIs whose mothers started ART post-conception (during pregnancy: weighted aHR 3.2; 95% CI 1.3–7.7; postpartum: weighted aHR 12.4; 95% CI 1.5–99.6) or when maternal VL at enrolment was unsuppressed (weighted aHR 15.7; 95% CI 7.8–31.3).

In the subcohort analysis, risk of any adverse outcome was associated with no disclosure by the mother of her status to her partner (weighted aHR 1.3; 95% CI 1.1–1.6) and unsuppressed maternal VL at enrolment (aHR 2.0; 95% CI 1.5–2.7).

In Figure 2, we present weighted 24-month survival plots. When the effects of all adverse outcomes were combined, HIV-free survival at 6, 12, 18 and 24 months was 93.8% (95% CI 92.5–95.1%), 86.2% (95% CI 84.4–87.9%), 80.6% (95% CI 78.5–82.6%) and 67.5% (95% CI 65.0–70.0%), respectively.

Starting ART pre-conception had the highest impact on reducing MTCT and infant death and ensuring HIV-free survival in HEIs. When HEIs lost to follow-up were excluded, the estimated 24-month survival of HEIs whose mothers started ART before pregnancy, during pregnancy, and postpartum and for whom it was unknown whether they started ART was 95.7% (95% CI 93.4–98.1%), 92.1% (95% CI 88.7–95.6%), 80.2% (95% CI 73.1–87.3%) and 60.2% (95% CI 39.7–81.8%), respectively (Figure 2c).

Secondary outcomes of HIV-infected infants

Among the 145 infants diagnosed at study enrolment, at the 24-month visit, 47 (32.4%) were on ART, 13 (9.0%)

were not on ART, 71 (49.0%) had been lost to follow-up and 14 (9.7%) had died. Among the 13 not on ART, one had stopped, three mothers reported not wanting the child to be on ART and nine did not have evidence of ART start. Among the seven infants diagnosed at the 12-month visit, by the 24-month visit two (28.6%) were on ART, two (28.6%) were not on ART and three (42.9%) had been lost to follow-up. The two not on ART at 12 months had not been documented to have received the test results or initiated ART by the 24 month study visit. All nine infants diagnosed at the final study visit were known to have started ART soon after this last visit.

DISCUSSION

In this nationally representative cohort, we observed that Malawi has achieved high PMTCT coverage. Almost half of mothers had started ART pre-conception, which had the greatest impact on reducing MTCT and ensuring HIV-free survival. MTCT at 24 months was low for a breastfeeding population (4.9%), infant mortality was low (1.3%) and HIV-free survival was 67.5%. After exclusion of HEIs lost to follow-up, the estimated 24-month survival of HEIs whose mothers started ART pre-conception was as high as 95.7%. However, over one-quarter of HEIs did not have a documented outcome at 24 months, and this may include infants who had died or become HIV infected.

Our study outcomes are consistent with 2016 national programme monitoring data that showed 5% infant positivity, 1% mortality, 56% HIV-free survival and 34% loss to follow-up among the national 24-month age cohort of 8769 HEIs [12]. Although our weighted proportions of HIV-free survival and loss to follow-up were better, our unweighted proportions were similar.

Loss to follow-up increased between 12 and 24 months. This may be explained by undocumented discharges after cessation of breastfeeding. While almost all HEIs were breastfed at enrolment, only 8% of all HEIs were still breastfed by 24 months, a finding in sharp contrast with the 23-month median duration of breastfeeding previously documented in a nationally representative survey [13]. With so few postnatal transmissions, we were not able to investigate factors associated with risk of transmission through breastfeeding.

We previously reported that early MTCT was strongly associated with lack of maternal ART during pregnancy, maternal ART initiation during versus before pregnancy, and nondisclosure by the mother of her HIV status to her partner [6]. Our current longer term survival analysis further strengthens the evidence that the timing of the start of maternal ART, especially prior to pregnancy, has the greatest impact on ensuring HIV-free survival in

HEIs. This is consistent with other studies from the region; in Zimbabwe, mothers starting ART pre-conception reduced the risk of MTCT in the 18 months postdelivery by 88% [9].

Primiparas and mothers with fewer children (fewer than four) in our study were at increased risk of adverse outcomes. Over 80% of all primiparas and almost 50% of mothers with fewer children in our study were young mothers (14–24 years), and young mothers accounted for just under a quarter of all mothers. Several studies have shown that pregnant adolescents and young mothers have unique challenges that hinder their access to HIV care and PMTCT services [14,15]. Further population-level reduction in MTCT may require additional effort to ensure that younger women with less experience in the PMTCT programme, identifiable as having lower parity, are retained in ART services during breastfeeding.

We further found that nondisclosure was associated with an increased risk of adverse outcomes over the breastfeeding period. Recent studies demonstrated that women who disclosed their HIV status to their partners achieved better PMTCT outcomes [16–18], and that women's fear of disclosure to their partner negatively impacted maternal uptake of and adherence to ART [19–21]. The dynamics of disclosure within couples in PMTCT care need to be contextualized within gender and cultural norms that present fewer opportunities for women to make autonomous decisions about their health.

In our study, uptake of infant NVP was independently associated with reduced risk of HIV transmission or infant death. This finding is consistent with evidence that neonatal prophylaxis is an important component of PMTCT and critical when the mother did not receive ART before giving birth [22].

We previously showed that nonsuppressed VL in the early postpartum period was predictive of early MTCT in this same cohort of women [23], and here we found that nonsuppressed VL in mothers at enrolment was further associated with an increased risk of all adverse events. Several studies highlight difficulties in sustaining both adherence and VL suppression throughout the postpartum period [8,24,25]. Further investigation is needed to understand and improve long-term VL suppression among HIV-infected women of reproductive age.

In our study, 145 HEIs were diagnosed with HIV infection during study enrolment (age 1–6 months); of these, five had already been diagnosed prior to the study and 16 seroconverted post-enrolment. As reported previously in the same cohort [2], uptake of EID prior to enrolment was low. Further efforts are needed to keep HEIs in PMTCT care during the breastfeeding period to ensure timely repeated HIV testing and prompt ART start when positive. Uptake of ART by HIV-infected infants in our study was

TABLE 2 Maternal and infant characteristics associated with adverse outcomes and HIV-free survival

Maternal and infant characteristics	Documented adverse outcomes versus HIV-free survival					
	Total cohort (<i>n</i> = 202 ^d HIV transmissions and deaths vs. 2024 ^d HIV-free survivals)			Subcohort ^a (<i>n</i> = 76 ^d vs. 601 ^d)		
	Crude HR (95% CI)	<i>P</i> -value	aHR ^b (95% CI)	<i>P</i> -value	aHR ^c (95% CI)	<i>P</i> -value
Maternal age at enrolment (1–6 months postpartum)						
≤ 24 years (young mothers)	1.4 (0.8–2.3)	0.21	NS		NS	
> 24 years	Ref					
Parity						
1	1.1 (0.6–2.1)	0.78	NS		NS	
2–3	1.6 (1.0–2.7)	0.07				
≥ 4	Ref					
Disclosure of HIV status to partner						
Mother disclosed HIV status to partner (before or after enrolment)	Ref		NS		NS	
No disclosure reported	1.2 (0.7–2.2)	0.52				
No partner	1.1 (0.6–2.0)	0.88				
Maternal ART start						
Before pregnancy	Ref		Ref		Ref	
During pregnancy	1.4 (0.7–2.6)	0.36	1.3 (0.6–2.5)	0.49	3.2 (1.3–7.7)	0.01
Postpartum (including newly diagnosed at study enrolment)	4.3 (2.1–8.6)	<0.001	2.5 (1.0–6.1)	0.05	12.4 (1.5–99.6)	0.02
Unknown when or if started	10.6 (3.9–28.5)	<0.001	5.5 (1.9–16.4)	0.002	1.8 (0.1–63.6)	0.85
Mother's adherence to ART at enrolment						
Missed 0–1 days of ART in the last month	Ref		Ref		NS	
Missed ≥ 2 days of ART in the last month	3.2 (1.6–6.3)	0.001	2.7 (1.4–5.0)	0.003		
Not on ART (yet, or stopped)	7.5 (4.4–12.8)	<0.001	1.5 (0.6–3.8)	0.40		
Infant received nevirapine prophylaxis (≤ 42 days from birth)						
Yes	Ref		Ref		NS	
No	4.7 (2.9–7.6)	<0.001	2.2 (1.2–3.9)	0.01		
Infant on cotrimoxazole prophylactic treatment at enrolment						
Yes	Ref		NS		NS	
No	1.9 (1.1–3.2)	0.02				
Missing, unknown	1.1 (0.4–2.9)	0.78				
Maternal viral load at enrolment (subcohort)						
< 1000 copies/mL	Ref				Ref	
> 1000 copies/mL	19.2 (10.5–35.3)	<0.001			15.7 (7.8–31.3)	<0.001

aHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; NS, not significant.

^aSubcohort analysis (including maternal viral load).

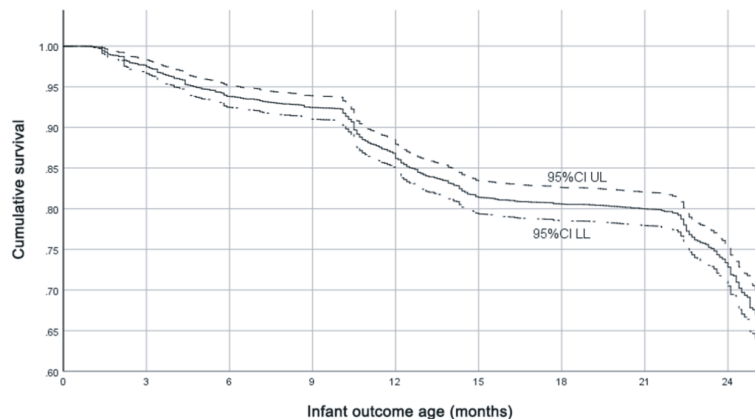
^bAdjusted for all variables in the model. Only significant associations are reported.

^cAdjusted for all variables in the model in the subgroup that include maternal viral load monitoring. Only significant associations are reported.

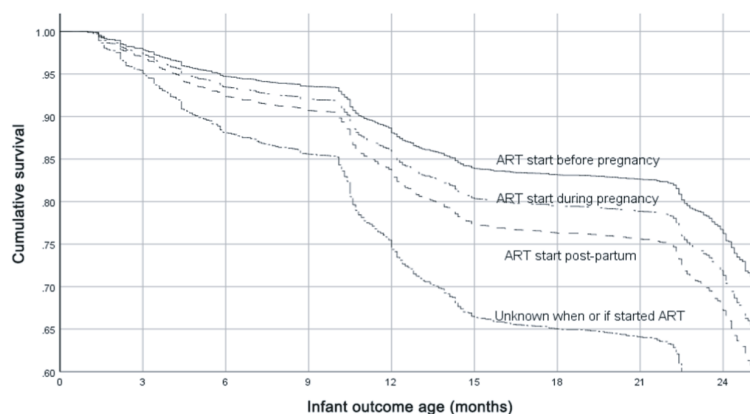
^dUnweighted n.

All adverse outcomes versus HIV-free survival					
Total cohort (1438 ^d HIV transmissions, deaths and loss-to-follow-up vs. 2024 ^d HIV-free survivals)				Subcohort ^a (n = 681 ^d vs. 601 ^d)	
Crude HR (95% CI)	P-value	aHR ^b (95% CI)	P-value	aHR ^c (95% CI)	P-value
1.5 (1.2–1.8)	<0.001	NS		NS	
Ref					
1.8 (1.3–2.3)	<0.001	1.6 (1.1–2.2)	0.02	NS	
1.6 (1.3–1.9)	<0.001	1.5 (1.2–1.9)	0.002		
Ref		Ref			
Ref		Ref		Ref	
1.4 (1.1–1.7)	<0.004	1.3 (1.1–1.6)	0.01	1.3 (1.1–1.6)	0.04
0.7 (0.5–0.9)	0.02	0.7 (0.5–0.9)	0.01	0.8 (0.6–1.1)	0.19
Ref		Ref		NS	
1.2 (1.0–1.5)	0.03	1.1 (0.9–1.4)	0.30		
1.5 (1.1–2.0)	0.02	1.4 (1.0–1.9)	0.07		
2.3 (1.2–4.4)	0.009	2.0 (1.0–3.9)	0.05		
Ref		Ref		NS	
1.7 (1.3–2.3)	0.001	1.7 (1.2–2.2)	0.002		
2.3 (1.6–3.3)	<0.001	1.7 (1.0–2.7)	0.05		
Ref		NS		NS	
1.8 (1.4–2.4)	<0.001				
Ref		NS		NS	
1.2 (1.1–1.5)	0.04				
1.5 (0.9–2.5)	0.10				
^a					
Ref					
2.6 (2.1–3.3)	<0.001			2.0 (1.5–2.7)	<0.001

- (a) 24-month HIV-free survival and time to all adverse outcomes (HIV-transmission, infant death or lost to follow-up)



- (b) 24-month HIV-free survival and time to all adverse outcomes by categories of timing of maternal ART initiation



- (c) 24-month HIV-free survival and time to known adverse outcomes (HIV-transmission or infant death - without those lost to follow-up) by categories of timing of maternal ART initiation

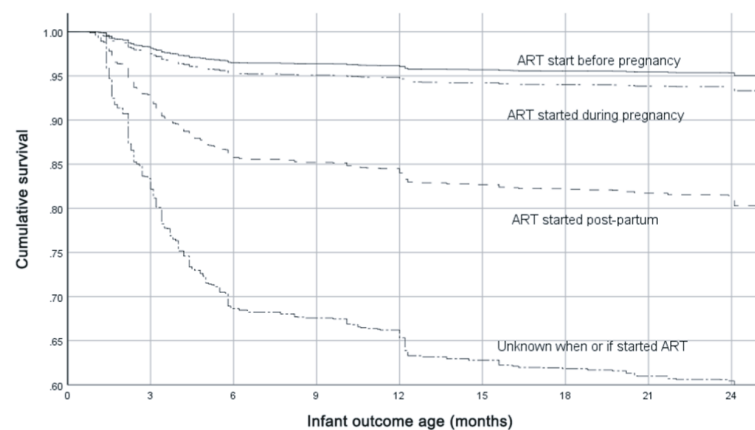


FIGURE 2 Weighted Kaplan–Meier survival plots, presenting 24-month survival and (a) time to HIV transmission, infant death or loss to follow-up, (b) time to HIV transmission, infant death or loss to follow-up by category of timing of maternal antiretroviral therapy (ART) initiation, and (c) time to HIV transmission or infant death (without those lost to follow-up) by category of timing of maternal ART initiation. (a) 24-month HIV-free survival and time to all adverse outcomes (HIV transmission, infant death or loss to follow-up). (b) 24-month HIV-free survival and time to all adverse outcomes by category of timing of maternal ART initiation. (c) 24-month HIV-free survival and time to known adverse outcomes (HIV transmission or infant death, without those lost to follow-up) by category of timing of maternal ART initiation

often delayed. Reasons for delayed ART start included delayed or unsuccessful tracing efforts for those who had not come back to the clinic to receive test results.

Strengths and limitations

This is the first nationally representative study that reports long-term effectiveness of universal ART for PMTCT throughout breastfeeding, and it provides estimates of and risks associated with 24-month cumulative MTCT, death and loss to follow-up. Because of the limitation to three study visits, we were not able to determine the timing of HIV transmission accurately. As a consequence of the few seroconversions, we could not investigate risk factors associated with transmissions during the breastfeeding period.

The study relied on routinely collected data and deliberately did not place dedicated study staff at health facilities as it aimed to evaluate real-life circumstances in the field. This resulted in regularly missed study procedures during routine clinic visits. Loss to follow-up was high but lower than anticipated in the original sample size calculations. Ministry of Health staff, burdened with a heavy routine clinic workload, also had to conduct study defaulter tracing activities, which may have contributed to high sustained loss to follow-up rates and delayed delivery of HIV test results and initiation of infant ART.

CONCLUSIONS

In a nationally representative longitudinal cohort study, we evaluated the effectiveness of the Malawi PMTCT programme. Implementation of universal and life-long ART has achieved low MTCT rates at 24 months for a breastfeeding population (4.9%). Starting ART pre-conception had the highest impact on reducing MTCT and ensuring HIV-free survival in HEIs up to 24 months of age. Other factors included high parity, disclosure of HIV status to the mother's partner, suppressed VL postpartum and adequate self-reported adherence. While infant mortality was low (1.3%), losses to follow-up were relatively high as the study reflected real-life circumstances. To reduce MTCT further, early HIV diagnosis, ART initiation prior to conception, and long-term engagement in HIV care need to be improved for Malawian women of childbearing age.

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CONFLICTS OF INTEREST

No conflicts of interest are declared.

AUTHOR CONTRIBUTIONS

Study design and methods were developed by MvL, BATB, JvO, ES, NW and ML. Data analysis was performed by MvL. Data interpretation was carried out by MvL, BATB, JvO, ES, AJ, TK, AA, RN, NW, EK and ML. Writing was completed by MvL, BATB and ML. All authors reviewed the final manuscript for submission.

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