Low detectable postpartum viral load is associated with HIV transmission in Malawi’s prevention of mother-to-child transmission programme

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Abstract
Introduction: In 2011, Malawi implemented “Option B+,” a test-and-treat strategy for the prevention of maternal to child transmission of HIV (PMTCT); however limited data on viral load (VL) suppression exist. We describe VL suppression in HIV-infected women at four to twenty-six weeks postpartum, factors associated with VL suppression and the impact of VL suppression levels on MTCT.

Methods: HIV-positive mothers at four to twenty-six weeks postpartum were enrolled in a nested cross-sectional study within the “National Evaluation of Malawi’s PMTCT Programme” cohort study between October 2014 and May 2016. HIV-exposed infants received HIV-1 DNA testing and venous samples determined maternal VL, classified as unsuppressed (>1000 copies/mL), low-detectable (40 to 1000 copies/mL) or undetectable (<40 copies/mL). Socio-demographic and PMTCT indicators were collected. Suboptimal adherence was defined as self-reported ≥2 days missed ART in the month prior to visit.

Results: Of the 1274 women, 1191 (93.5%) knew their HIV status and 1154/1191 (96.9%) were on ART. VL was available for 1124/1154 (97.4%) of women on ART: 988/1124 (87.9%) had VL suppression of whom 86 (8.7%) had low-detectable and 902 (91.3%) undetectable VL. Suboptimal adherence was associated with unsuppressed VL (vs. suppressed VL; aOR 3.1, 95% CI 2.0 to 4.9; p < 0.001). Women with low-detectable VL were more likely to be adolescent (vs. undetectable VL; aOR 3.0, 95% CI 1.4 to 6.6), on ART <6 months (aOR 4.4, 95% CI 2.3 to 8.6), report suboptimal adherence (aOR 2.1, 95% CI 1.1 to 3.8; p = 0.02), and less likely to have primary or secondary education (vs. none; aOR 0.3, 95% CI 0.2 to 0.7 or aOR 0.3, 95% CI 0.1 to 0.6). MTCT ratios among women on ART who had undetectable VL, low-detectable VL and unsuppressed VL were 0.9% (8/902; 95% CI 0.3 to 1.5), 7.0% (6/86; 95% CI 1.5 to 12.5) and 14.0% (19/136; 95% CI 8.1 to 20.0). Unsuppressed VL and low-detectable VL (vs. undetectable VL) increased the risk of MTCT 17-fold (aOR 17.4, 95% CI 7.4 to 41.1; p = 0.002) and ninefold (aOR 8.5, 95% CI 2.9 to 25.2; p < 0.001).

Conclusions: Unsuppressed and low-detectable VL was strongly predictive of MTCT among women on ART and associated with suboptimal adherence. This urges further consideration of optimal VL monitoring and target levels to reach elimination of paediatric infection.

Keywords: viral load suppression; HIV; prevention of maternal to child transmission; antiretroviral therapy; HIV transmission; Option B+

Received 3 October 2018; Accepted 8 May 2019

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1 | INTRODUCTION

In 2011, Malawi implemented “Option B+,” a universal test and treat strategy for all pregnant and breastfeeding women for the prevention of mother-to-child-transmission (PMTCT) of HIV [1,2]. Option B+ has led to markedly increased rates of antiretroviral therapy (ART) initiation of among HIV-infected women of reproductive age [3,4]. However, little is known about the degree to which women on ART achieve sustained viral load (VL) suppression during pregnancy, delivery and breastfeeding, which is a key determinant of mother-to-child-transmission (MTCT).

Since 2015, routine VL monitoring in Malawi has been challenged by human resource shortages, difficulties in sample transportation to centralized laboratories, and laboratory capacity [5]. Furthermore, national ART programme VL suppression estimates do not accurately capture women in Option B+ as VL testing is rarely performed during pregnancy or breastfeeding [4]. Regionally, countries face similar challenges in estimating VL suppression in the Option B+ population and there is a lack of consensus on best practices of VL monitoring for women initiating ART during pregnancy or breastfeeding [6]. Extrapolating from study settings, VL suppression estimates are 84.6% among women enrolled in
Option B+ during late pregnancy/early postpartum in Rwanda and 89.6% in Uganda among women starting ART in pregnancy and retained in care at five years [7,8].

Further complicating an understanding of how VL suppression impacts MTCT within Option B+ is the variation in VL suppression definitions throughout the region. In Malawi, VL suppression is defined as <1000 copies/mL [9], yet a relevant proportion of MTCT occurred in women enrolled in Option B+ in South Africa with low-detectable VL levels, that is, between 40 and 1000 copies/mL [10]. Few PMTCT programmes, including the Malawi HIV programme, distinguish between low-detectable and undetectable VL levels.

The National Evaluation of Malawi’s PMTCT Programme (NEMAPP) study launched in 2014 to evaluate the effectiveness of Option B+ by enrolling HIV-infected women and their infants at four to twenty-six weeks postpartum and following them for 24 months. Within this nationally representative cohort, uptake of PMTCT services was very high: 97.8% of women knew their HIV status at enrolment and 96.3% of these were on ART [11]. Here, we describe VL suppression rates, factors associated with VL suppression and MTCT ratios stratified by low-detectable, undetectable and unsuppressed VL, at four to twenty-six weeks postpartum among a sample of women enrolled in the NEMAPP study. These findings are relevant for Malawi’s performance against the UNAIDS 90-90-90 targets by providing insight into the third “90” among pregnant and breastfeeding women on ART [12].

2 | METHODS

This is a nested cross-sectional study of HIV-infected mothers presenting with their four to twenty-six week old infants at outpatient clinics who were enrolled in longitudinal follow-up in the National Evaluation of the Malawi PMTCT Programme (NEMAPP) study between October 2014 and May 2016. NEMAPP used a multistage cluster design to sample 54 sites across Malawi [13] and this sub-set was derived using probability proportionate-to-size sampling methods to select 13 sites across the eight districts from the original sites. Women in these selected sites were simultaneously consented for enrolment in both the main study and in this subset for intensive clinical and laboratory monitoring. All mother-infant pairs were followed up at 12 and 24 months.

The study period occurred three years after the national implementation of “Option B+” PMTCT guidelines in Malawi which provided lifelong ART (i.e. tenofovir/lamivudine/efavirenz) for all pregnant and breastfeeding women. Mothers (or guardians) with four to twenty-six week infants were screened for HIV infection by the study team and 3456 HIV-positive mothers (or guardians) with HIV-exposed infants were consented for enrolment in the main study. A sample of 1324 HIV-positive mothers was calculated to estimate VL suppression based on an estimated 50% suppression rate, 50% loss to follow-up at 24 months and a precision of 2.5% with a 95% confidence interval (95% CI) and an assumed design effect of 2.0. Guardians were excluded from the current analysis (Figure 1).

Included mothers were interviewed using structured questionnaires by trained health facility staff to obtain information about age, parity, education, HIV status at screening, uptake of MTCT/ART, adherence to treatment (self-reported number of days missed ARVs in the last month), birthweight of infant, uptake of infant nevirapine prophylaxis and breastfeeding practices. When possible, mothers’ health booklets were checked for accuracy of responses.

A qualitative HIV-1 DNA polymerase chain reaction (COBAS AmpliPrep/COBAS TaqMan Qualitative Assay Version 2.0, detection level 221 copies/mL; Roche Diagnostics, USA) test was performed on all HIV-exposed infant dried blood spot (DBS) samples to determine HIV infection at the time of enrolment into NEMAPP (as part of study procedures and outside of national PMTCT programme testing). Within this subset, maternal HIV viral load (VL) testing was conducted at enrolment on venous samples (Abbott Real-Time HIV-1 Assay, Abbott Laboratories, Chicago, IL) of all women regardless of ART status. VL suppression is defined as HIV-1 RNA <1000 copies/mL as per the Malawi national HIV guidelines [1]. We further categorized VL results as “undetectable” (<40 copies/mL), “low-detectable” (40 to 1000 copies/mL) and “unsuppressed” (>1000 copies/mL), with “suppressed VL” being the inverse, i.e. all women with <1000 copies/mL.

Missing data were treated as additional categories. Crude percentages were calculated and comparisons between groups made using chi-square tests for categorical variables and non-parametric tests for medians, using normal approximations (Wald) methods to calculate confidence intervals. Multivariable logistic regression analysis was used to identify characteristics associated with unsuppressed versus suppressed VL, with low-detectable versus undetectable VL, and with MTCT. Univariate odds ratios (OR) with 95% CI were calculated for each variable in the model using normal approximation (Wald) methods. Adjusted OR (aOR) with 95% CI were calculated for each model after adjustment for age, parity, education, time on ART, number of days missed ARV’s in last month and exposure to PMTCT in a previous pregnancy. In addition, birthweight, uptake of infant nevirapine, exclusive breastfeeding and VL categories were included in the model for MTCT. All variables were simultaneously entered in the logistic regression model and tested for removal through backward stepwise selection. A 0.05 significance level was set for all statistical testing. Analyses were conducted using IBM SPSS Statistics 24 (IBM, Armonk, NY, USA).

Ethical approval was received from Malawi’s National Health Sciences Research Committee (#1262) and the University of Toronto (#30448). The US Centers for Disease Control and Prevention (CDC) reviewed and approved as research according to human research protection procedures (#2014-054-7), but was not engaged. All participants provided written informed consent.

The funding source for this study was the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) and they had no direct role in study design, implementation, analysis or preparation/submission of this manuscript. The author acknowledges full access to all the data and final responsibility for submission.

3 | RESULTS

A total of 1274 mother-infant pairs were included in this study (see Figure 1). Table 1 describes the characteristics of mothers: median age was 29 years (IQR 23 to 33) and
median parity was three births (IQR 2 to 4). The majority had no formal education or primary school only (836/1274; 65.6%).

Overall, 1191 (93.5%) women knew their HIV status at enrolment and 1154 (96.9%) of these women were on ART. Among women on ART, 573 (49.7%) started ART before pregnancy, 569 (49.3%) during pregnancy, and 12 (1.0%) started postpartum. The median duration on ART for those starting before pregnancy, during pregnancy, and postpartum was 39.3 months (IQR 18.3 to 59.0), 6.3 months (4.6 to 8.5), and 1.2 months (0.5 to 2.9) respectively (See Table 2). Among women on ART, 910 (78.9%) reported missing no days of ART in the last month.

Among the 120 women who reported not being on ART at enrolment, 16 (13.3%) had started but stopped ART, 21 (17.5%) did not wish to disclose their HIV status to the study team prior to HIV testing during screening and 83 women (69.2%) were newly diagnosed HIV infections (i.e. either HIV negative or unknown prior to testing HIV positive at enrolment).

Of the 1274 infants born, 235 (18.4%) were low birthweight (<2.5Kg), of which 7 (3.0%) were very low birthweight (<1.5 kg). 91.1% of infants received nevirapine prophylaxis and 91.4% were exclusively breastfed until enrolment.

VL results were available for 1241 (97.4%) women: 1124/1154 (97.4%) of women on ART and 117/120 (97.5%) of women not on ART (see Table 2). Among women on ART with available VL (N = 1124), 988 (87.9%) achieved VL suppression, of whom 902 (91.3%) had undetectable VL and 86 (8.7%) had low-detectable VL.

Achieving undetectable VL occurred more in women who started ART prior to pregnancy compared to during

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*13 sites were purposefully selected among the 54 randomly selected facilities included in a national evaluation and included all hospitals and large facilities contributing to an equal distribution of participants in the geographical regions.*
pregnancy (469/556: 84.4% vs. 424/556: 76.3%; p = 0.001).

Conversely, having low-detectable VL occurred more in women who started ART during pregnancy compared to those starting before (58/556:10.4% vs. 25/556: 4.5%; p < 0.001).

Among women who started ART postpartum, 100% (12/12) achieved VL suppression and 9/12 (75%) achieved undetectable VL. There was no significant difference in the proportion of women with unsuppressed VL between those who started ART prior to this pregnancy and those who started during the pregnancy (62/556: 11.2% vs. 74/556: 13.3%; p = 0.27).

The majority of women not on ART had unsuppressed VL (89/117: 76.1%) and had significantly higher median VL than women on ART (see Table 2; p = 0.001). The majority of women not on ART and with unsuppressed VL were those with newly diagnosed infections (67/89; 75.3%) at the time of enrolment. Of the 28 (24.0%) women not on ART but who had either suppressed or low-detectable VL, 11 (39.3%) did not reveal their HIV status (or ART use) to the study team at enrolment and 4 (14.3%) had started or stopped ART (date of stopping not available).

Table 3 describes MTCT for women on ART and those not on ART stratified by viral load categories. Of the 34 transmissions occurring among women on ART, 6 (17.6%) occurred in women with low detectable VL and 19 (55.9%) occurred in women with unsuppressed VL. MTCT ratios among women on ART with undetectable VL, low detectable VL and unsuppressed VL were 0.9% (8/902; 95% CI 0.3 to 1.5), 7.0% (6/86; 95% CI 1.6 to 12.4) and 14.0% (19/136; 95% CI 8.1 to 19.8) respectively.

Among women not on ART, MTCT ratios for those with undetectable VL, low detectable VL and unsuppressed VL were 14.3% (2/14; 95% CI 0.0 to 32.6), 21.4% (3/14; 95% CI 0.0 to 42.9) and 30.3% (7/23; 95% CI 20.8 to 39.9) respectively. Among the 32 infections occurring in women not on ART, 24 (75%) occurred among women with new infections at the time of study (1 had low-detectable virus and 20 (83.3%) had unsuppressed VL) and the MTCT rate among new infections overall was 24/83 (28.9%). There were significant

Table 1. Characteristics of women included in the study

| Characteristic                                                                 | n     | n = 1274 |
|--------------------------------------------------------------------------------|--------|----------|
| **Mother age in years, median (IQR)**                                          | 1272   | 29 (23 to 33) |
| **Mother’s age in years, %**                                                   |        |          |
| ≤19                                                                            | 86     | 6.8      |
| 20 to 24                                                                       | 284    | 22.3     |
| 25 to 29                                                                       | 338    | 26.5     |
| ≥30                                                                            | 564    | 44.3     |
| Missing                                                                        | 2      | 0.2      |
| **Infant age at enrolment in months, median (IQR)**                            | 1274   | 1.8 (1.5 to 3.1) |
| **Parity, median (IQR)**                                                       | 1272   | 3 (2 to 4) |
| **Level of education, %**                                                      |        |          |
| None                                                                           | 114    | 8.9      |
| Primary education                                                              | 722    | 56.7     |
| Secondary education                                                            | 416    | 32.7     |
| Post-secondary education                                                       | 22     | 1.7      |
| **Maternal HIV status at time of study screening, % (four to twenty-six weeks postpartum)** | 1191   | 93.5     |
| **Exposure to PMTCT in a previous pregnancy**                                  |        |          |
| None                                                                           | 734    | 57.6     |
| Short course PMTCT                                                             | 123    | 9.7      |
| before Option B+ (sdNVP or AZT)                                                | 396    | 31.1     |
| Triple ART (for own health or option B+)a                                      |        |          |
| Missing                                                                        | 21     | 1.6      |
| **Maternal ART Status, %**                                                     |        |          |
| On ART (started before last pregnancy)                                         | 573    | 45.0     |
| On ART (started during last pregnancy)                                        | 569    | 44.7     |
| Started but Stopped ART                                                        | 12     | 0.9      |
| Unknown, did not want to reveal                                                | 16     | 1.3      |
| Did not start ART yet (newly diagnosed)                                        | 63     | 5.0      |
| **Time on ART in months (at time of study)**                                   | 940    | 9.9 (5.7 to 44.1) |
| (at time of study) among those on ART, %                                       |        |          |
| ≤2.0                                                                           | 36     | 3.1      |
| 2.1 to 6.0                                                                    | 225    | 19.5     |
| 6.1 to 12.0                                                                   | 227    | 19.7     |
| 12.1 to 18.0                                                                  | 38     | 3.3      |
| 18.1 to 24.0                                                                  | 42     | 3.6      |
| ≥24                                                                           | 372    | 32.2     |
| Missing                                                                        | 214    | 18.5     |

Number of days having missed ART in the last month, among those on ART

| Days                                | n     | n = 1274 |
|-------------------------------------|-------|----------|
| 0                                   | 910   | 78.9     |
| 1 day                               | 93    | 8.1      |

Table 1. (Continued)

| Characteristic                                                                 | n     | n = 1274 |
|--------------------------------------------------------------------------------|--------|----------|
| ≥2 days                                                                          | 136    | 11.8     |
| Missing                                                                          | 15     | 1.3      |
| **Birthweight of index infant**                                                  |        |          |
| Low birthweight, 1.5 to 2.5 kg                                                   | 235    | 18.4     |
| Normal birthweight, 2.5 to 4.2 kg                                                | 993    | 77.9     |
| Missing                                                                          | 46     | 3.6      |
| **Infant nevirapine prophylaxis received by exposed infants**                    |        |          |
| Received nevirapine                                                              | 1161   | 91.1     |
| Did not receive nevirapine                                                       | 113    | 8.9      |
| **Exclusive breastfeeding (reported no other food)**                             |        |          |
| Yes                                                                               | 1164   | 91.4     |
| No                                                                                | 108    | 8.5      |
| Missing                                                                          | 2      | 0.2      |

aStarted prior to or during previous pregnancy, independent of current ART status. 

pregnancy (469/556: 84.4% vs. 424/556: 76.3%; p = 0.001). Conversely, having low-detectable VL occurred more in women who started ART during pregnancy compared to those starting before (58/556:10.4% vs. 25/556: 4.5%; p < 0.001). Among women who started ART postpartum, 100% (12/12) achieved VL suppression and 9/12 (75%) achieved undetectable VL. There was no significant difference in the proportion of women with unsuppressed VL between those who started ART prior to this pregnancy and those who started during the pregnancy (62/556: 11.2% vs. 74/556: 13.3%; p = 0.27).

The majority of women not on ART had unsuppressed VL (89/117: 76.1%) and had significantly higher median VL than women on ART (see Table 2; p = 0.001). The majority of women not on ART and with unsuppressed VL were those with newly diagnosed infections (67/89; 75.3%) at the time of enrolment. Of the 28 (24.0%) women not on ART but who had either suppressed or low-detectable VL, 11 (39.3%) did not reveal their HIV status (or ART use) to the study team at enrolment and 4 (14.3%) had started or stopped ART (date of stopping not available).

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Among women not on ART, MTCT ratios for those with undetectable VL, low detectable VL and unsuppressed VL were 14.3% (2/14; 95% CI 0.0 to 32.6), 21.4% (3/14; 95% CI 0.0 to 42.9) and 30.3% (7/23; 95% CI 20.8 to 39.9) respectively. Among the 32 infections occurring in women not on ART, 24 (75%) occurred among women with new infections at the time of study (1 had low-detectable virus and 20 (83.3%) had unsuppressed VL) and the MTCT rate among new infections overall was 24/83 (28.9%). There were significant
differences in both median VL and MTCT between women on ART and those not on ART with unsuppressed VL (median VL 11,618 vs. 34,349, \( p = 0.005 \) and 14.0 vs. 30.3, \( p = 0.003 \) respectively).

In multivariable analysis, women with unsuppressed VL were more likely than women with suppressed VL to report suboptimal adherence (aOR 3.1, 95% CI 2.0 to 4.9; \( p < 0.001 \)) when adjusted for age, parity, education, time on ART and previous exposure to PMTCT/ART. Women with low-detectable VL were more likely than those with undetectable VL to be adolescent (aOR 3.0, 95% CI 1.4 to 6.6), on ART for less than six months (aOR 4.4, 95% CI 2.3 to 8.6) and have suboptimal adherence (aOR 2.1, 95% CI 1.1 to 3.8; \( p = 0.02 \)), and less likely to have primary or secondary education versus no education (aOR 0.3, 95% CI 0.2 to 0.7 and aOR 0.3, 95% 0.1 to 0.6 respectively; see Table 4).

Table 5 shows multivariable analysis of characteristics associated with MTCT among women on ART. Compared to having undetectable VL, unsuppressed VL and low-detectable VL increased the odds of MTCT 17-fold (aOR 17.4, 95% CI 7.4 to 41.1; \( p = 0.002 \)) and ninefold (aOR 8.5, 95% CI 2.9 to 25.2; \( p < 0.001 \)).

### DISCUSSION

In this nationally representative cohort of HIV-infected women enrolled in Malawi’s PMTCT programme, the postpartum viral load (VL) suppression ratio for women on ART is approaching the third UNAIDS 90-90-90 goal of 90% VL suppression. While not being on ART was associated with detectable VL and MTCT, among those on ART, unsuppressed VL and low-detectable VL remained the strongest predictor of transmission. Almost 9% of women traditionally classified as reaching VL suppression (<1000 copies/mL) in fact had low-detectable levels of viraemia (40 to 1000 copies) and accounted for more than one in six of all MTCT infections occurring in women on ART. Suboptimal adherence was the strongest predictor of both low-detectable VL and unsuppressed VL, along with adolescent age, lower levels of education and less time on ART.

Our VL suppression estimate indicates that the Malawi PMTCT programme is close to reaching the final UNAIDS goal of 90% among HIV-infected pregnant and breastfeeding women on ART. Similar estimates are documented in the postpartum period in three Option B+ study cohorts: 81.2%
Table 4. Factors associated with unsuppressed (>1000) versus suppressed (<1000) and low-detectable (VL 40 to 1000) versus undetectable (<40) maternal viral load among Malawian women on ART four to twenty-six weeks postpartum (for whom VL available)

|                      | Unsuppressed (>1000) vs. suppressed (<1000) VL | Low-detectable (40 to 1000) vs. undetectable (<40) VL |
|----------------------|-----------------------------------------------|--------------------------------------------------|
|                      | n/n %                                         | n/n %                                           |
|                      | Univariate (unadjusted)                      | Multivariable (adjusted)                        | Univariate (unadjusted)                      |
|                      | OR (95% CI) p-value                          | aOR (95% CI)* p-value                           | OR (95% CI) p-value                          |
|                      |                                               |                                                 |                                               |
| Total                | 136/1124 12                                   | 86/988 9                                       |
| Mother’s age in years|                                               |                                                 |                                               |
| ≤19                  | 9/72 13                                      | 12/194 10                                     |
| 20 to 24             | 36/230 16                                    | 19/194 10                                     |
| ≥30                  | 33/297 11                                    | 27/264 10                                     |
| Missing              | 0/2 0                                        | 28/465 6                                      |
| Parity               |                                               |                                                 |                                               |
| 1                    | 22/159 14                                    | 14/137 10                                     |
| 2 to 3               | 68/544 13                                    | 49/476 10                                     |
| ≥4                   | 46/419 11                                    | 33/373 6                                      |
| Missing              | 0/2 0                                        | 0/2 0                                          |
| Level of education   |                                               |                                                 |                                               |
| None                 | 9/100 9                                      | 16/91 18                                      |
| Primary education    | 84/632 13                                    | 44/458 8                                      |
| Secondary or post-secondary education | 43/392 11 | 26/349 7                                      |
|                      |                                               |                                                 |                                               |
| Time on ART (months) |                                               |                                                 |                                               |
| <6                   | 22/254 9                                     | 39/232 17                                     |
| 6 to 12              | 25/221 11                                    | 14/196 7                                      |
| 12 to 24             | 8/79 10                                      | 2/71 3                                        |
| ≥24                  | 41/363 11                                    | 14/322 4                                      |
| Missing              | 40/207 19                                    | 17/167 10                                     |
| No. of days having missed ARVs in the last month |                                               |                                                 |                                               |
| 0                    | 89/886 10                                    | 68/797 9                                      |
| 1 day                | 8/90 9                                       | 1/82 1                                         |
| ≥2 days              | 35/134 26                                    | 17/99 17                                      |
| Missing              | 4/14 29                                      | 0/10                                           |                                               |
Among Zimbabwean women at four to twelve weeks [14], 84% among Malawian women at six months postpartum [15] and 84% among Rwandan women in late pregnancy/early postpartum [7]. Among women who achieve VL suppression, the Malawi PMTCT programme shows remarkable reductions in MTCT. This impact is greatest among women on ART reaching undetectable VL where the MTCT ratio (i.e. <1%) approaches estimates in higher resource settings [16,17]. However, we identify a strong association between any detectable VL in the early postpartum period and MTCT: women on ART with unsuppressed VL had a 17-fold increased risk of MTCT and those with low-detectable VL had a ninefold increased risk. Notably, almost 9% of women traditionally classified by WHO guidelines as suppressed VL (i.e. <1000 copies/mL) had a low-detectable VL and accounted for almost 20% of all transmissions. Limited data exist on the role of low level viraemia among women on ART during pregnancy, delivery or breastfeeding in MTCT risk in the region, however one recent South African cohort of women initiated on ART during pregnancy demonstrated an increased risk of MTCT for women with low detectable VL versus those with undetectable VL (<50 copies/mL; 2 vs. 0.2%) at eight weeks of age [10]. We estimate that in Malawi, women with low-detectable viraemia (vs. undetectable VL) on ART in the early postpartum period contribute an excess 460 new infant HIV infections yearly (i.e. 60 infections/100,000 births per annum) [18]. These excess infections alone place Malawi above the level of control as outlined by the WHO (50 per 100,000 live births) for the elimination of MTCT and highlights the high priority of identifying detectable VL levels during pregnancy, delivery and breastfeeding [19]. Challenges exist to determining low-detectable levels in much of the region, and currently in Malawi most VL tests are done using DBS, which has a viral load detection limit of 1000 copies/mL. These data contribute to an urgent consideration of VL target levels to eliminate MTCT in this region.

While we cannot comment on the trajectory of VL levels for women on ART with low-detectable or unsuppressed virus during pregnancy and delivery, our findings contribute to regional discussions regarding the impact that VL monitoring in pregnancy/breastfeeding could have on improving MTCT rates [6,20]. Currently in the region, VL monitoring is rarely coordinated with delivery in pregnant women living with HIV and in Malawi guidelines still recommended VL testing at six months after ART initiation and then every two years [1]. In routine ART programmes, VL monitoring and suppression “thresholds” trigger a cascade of interventions by clinicians to improve patient outcomes. These include intensification of efforts to first support adherence and second, after sustained elevated VL, to consider resistance testing to guide switching regimens. The importance of having stratified VL information for clinicians working with women initiating ART in pregnancy and breastfeeding to trigger this cascade of interventions should be considered a priority, especially given the short timelines associated with the PMTCT cascade of HIV detection, ART initiation and ultimately delivery of an infant and exposure to breastfeeding. These findings call for urgent discussion about timing and frequency of VL monitoring for pregnant women.

Here, we found that women on ART with both unsuppressed and low-detectable VLs were more likely to self-report suboptimal adherence in the past month which

| Exposure to PMTCT | Univariate (unadjusted) | Multivariable (adjusted) |
|-------------------|-------------------------|--------------------------|
| None              | 71/611                  | 0.9 (0.5 to 1.7)         |
| Short course      | 13/120                  | 1.2 (0.8 to 1.8)         |
| Option B          | 51/373                  | 1.2 (0.8 to 1.8)         |
| Missing           | 1/20                    | 0.4 (0.1 to 3.0)         |

All variables were simultaneously entered in the logistic regression model as the first step and tested for removal one by one. In the multivariable analysis, only variables with significant associations were included in the final model. Results are presented as univariate odds ratios (OR) and multivariable adjusted odds ratios (aOR) with 95% confidence intervals (CI).
Table 5. Factors associated with MTCT among Malawian women on ART

| Variable                                      | All n = 34/1154 | 2.9% | Univariate (unadjusted) | p-value | Multivariate (adjusted) | p-value |
|-----------------------------------------------|----------------|------|-------------------------|---------|-------------------------|---------|
|                                               |                |      | OR (95% CI)             | p-value | aOR (95% CI)           | p-value |
| Mother’s age in years                         |                |      |                        |         |                        |         |
| ≤19                                           | 4/74           | 5.4% | 2.7 (0.8 to 8.8)       | 0.09    |                        |         |
| 20 to 24                                      | 8/234          | 3.4% | 1.7 (0.7 to 4.2)       | 0.27    |                        |         |
| 25 to 29                                      | 11/309         | 3.6% | 1.8 (0.8 to 4.1)       | 0.19    |                        |         |
| ≥30                                           | 11/535         | 2.1% | ref                     |         |                        |         |
| Missing                                       | 0/2            | 0%   | ref                     |         |                        |         |
| Parity                                        |                |      |                        |         |                        |         |
| 1                                             | 5/163          | 3.1% | 1.2 (0.4 to 3.5)       | 0.74    |                        |         |
| 2 to 3                                        | 18/560         | 3.2% | 1.3 (0.6 to 2.7)       | 0.55    |                        |         |
| ≥4                                            | 11/429         | 2.6% | ref                     |         |                        |         |
| Missing                                       | 0/2            | 0%   | ref                     |         |                        |         |
| Level of education                            |                |      |                        |         |                        |         |
| None                                          | 3/103          | 2.9% | ref                     |         |                        |         |
| Primary education                             | 23/650         | 3.5% | 1.2 (0.4 to 4.1)       | 0.75    |                        |         |
| Secondary education                           | 8/379          | 2.1% | 0.7 (0.2 to 2.8)       | 0.63    |                        |         |
| Post-secondary education                      | 0/22           | 0%   | ref                     |         |                        |         |
| Time on ART (months)                          |                |      |                        |         |                        |         |
| <6                                            | 10/261         | 3.8% | 2.4 (0.9 to 6.8)       | 0.09    |                        |         |
| 6 to 12                                       | 10/227         | 4.4% | 2.8 (1.0 to 7.8)       | 0.05    |                        |         |
| 12 to 24                                      | 2/80           | 2.5% | 1.6 (0.3 to 7.9)       | 0.59    |                        |         |
| >24                                           | 6/372          | 1.6% | ref                     |         |                        |         |
| Missing                                       | 6/214          | 2.8% | 1.8 (0.6 to 5.5)       | 0.33    |                        |         |
| Nr of days having missed ART in the last month|                |      |                        |         |                        |         |
| 0                                             | 25/910         | 2.7% | ref                     |         |                        |         |
| 1 day                                         | 3/93           | 3.2% | 1.2 (0.3 to 4.0)       | 0.79    |                        |         |
| ≥2 days                                       | 5/136          | 3.7% | 1.4 (0.5 to 3.6)       | 0.55    |                        |         |
| Missing                                       | 1/15           | 6.7% | 2.5 (0.3 to 20.0)      | 0.38    |                        |         |
| Birthweight of index infant                   |                |      |                        |         |                        |         |
| Low birthweight, 1.5 to 2.5 kg                | 7/203          | 3.4% | 1.2 (0.5 to 2.8)       | 0.65    |                        |         |
| Normal birthweight, 2.5 to 4.2 kg             | 26/912         | 2.9% | ref                     |         |                        |         |
| Missing                                       | 1/39           | 2.6% | 0.9 (0.1 to 6.8)       | 0.91    |                        |         |
| Infant nevirapine prophylaxis received by exposed infants | 32/1118 | 2.9% | ref                     |         |                        |         |
| Received nevirapine                           | 2/36           | 5.6% | 2.0 (0.5 to 8.7)       | 0.36    |                        |         |
| Did not receive nevirapine                    |                |      |                        |         |                        |         |
| Exclusive breastfeeding (reported no other food)|            |      |                        |         |                        |         |
| Yes                                           | 27/1064        | 2.5% | ref                     |         |                        |         |
| No                                            | 6/88           | 6.8% | 2.8 (1.1 to 7.0)       | 0.03    |                        |         |
| Missing                                       | 1/2            | 50%  | 38.4 (2.3 to 630.3)    | 0.01    |                        |         |
| Previous exposure to PMTCT                    |                |      |                        |         |                        |         |
| No previous exposure to ART/PMTCT             | 22/628         | 3.5% | ref                     |         |                        |         |
| Previous short course (sdNVP or AZT) for PMTCT| 5/121          | 4.1% | 1.2 (0.4 to 3.2)       | 0.73    |                        |         |
| Previous triple ART prior to pregnancy        | 7/384          | 1.8% | 0.5 (0.2 to 1.2)       | 0.13    |                        |         |
| Missing                                       | 0/21           | 0%   | ref                     |         |                        |         |
| Viral load among all                          |                |      |                        |         |                        |         |
| <40                                           | 8/902          | 0.9% | ref                     |         |                        |         |
| 40 to 1000                                    | 6/86           | 7.0% | 8.4 (2.8 to 24.8)      | <0.001  | 8.5 (2.9 to 25.2)      | <0.001  |
| >1000                                         | 19/136         | 14.0%| 18.1 (7.8 to 42.4)     | <0.001  | 17.4 (7.4 to 41.1)     | 0.002   |
| Missing                                       | 1/30           | 3.3% | 3.9 (0.5 to 31.8)      | 0.21    | 3.4 (0.4 to 28.2)      | 0.27    |

All variables were simultaneously entered in the logistic regression model as the first step and tested for removal one by one. In the multivariable analysis, only variables with significant associations in the last step are shown.

Controlled for all other variables shown in this table.
supports recent findings in South Africa, in the context of Option B+, that longitudinal self-reported adherence could predict episodes of viraemia in pregnant and postpartum women [21]. This suggests that self-report may be useful in this programmatic context to identify women needing intensified adherence interventions to improve VL suppression, even in the absence of routine VL testing during pregnancy. In Malawi, national guidelines state adherence should be ascertained at all clinical appointments, followed by group counselling or intensified adherence support if adherence is inadequate. However, studies of similar populations in the region describe ongoing challenges for women in adherence during pregnancy and breastfeeding [22,23]. While limited evidence exists that links specific adherence interventions to VL suppression targets in this population, some studies have shown promising interventions for adherence interventions such as counselling or peer support mechanisms in the general population [24].

The ideal timing and frequency of VL measurement during pregnancy and breastfeeding also remains unclear, including an understanding of how long it would take to reach undetectable VL with intensified adherence interventions. In a South African cohort of women initiated on ART in pregnancy, time to undetectable VL was 28 days and we similarly report that 100% of women in this cohort starting ART postpartum (median duration 1.2 months) had reached VL suppression and 75% had undetectable VL [10]. By increasing VL availability before delivery (i.e. <4 weeks prior) improvements may be made in adherence, VL suppression rates and infant outcomes. Furthermore, consideration could be made for those women who are identified with detectable VL for intensifying infant ART prophylaxis at birth and/or to receive ongoing monitoring and adherence interventions for maintaining VL suppression during breastfeeding, and or to receive resistance testing to guide potential regimen switches.

We additionally note that achieving undetectable VL was more challenging for adolescents and for women who had less education and less time on ART. Regional evidence highlights that adolescents are more likely to miss steps in the PMTCT cascade and suboptimally engage in care, yet studies supporting adherence interventions purposefully targeting pregnant adolescents are extremely limited [11,25–27]. Interventions to improve adherence, especially those appropriately targeted to age and education level, and or the addition of intensified prophylaxis for infants (PREP) of women with any detectable VL prior to delivery or in the early postpartum period have not yet been assessed but could help inform PMTCT programmes regarding VL monitoring frequency and suppression targets.

## 6 | CONCLUSIONS

In this nationally representative cohort of HIV-infected women enrolled in Malawi’s Option B+ programme, postpartum viral load (VL) suppression for women on ART is approaching the third UNAIDS 90-90-90 goal of 90% VL suppression. However, we identify a strong association between any detectable VL in the early postpartum period and a considerable population risk of MTCT. These findings call for urgent discussion about the availability, timing and frequency of VL monitoring in Malawi and whether VL monitoring should be able to detect lower levels of viraemia (i.e. <40 or < 20 copies/mL). Additionally, more research is required that explores optimal timing of VL measurement and effective interventions for achieving VL suppression in this population and the impact on eliminating paediatric HIV.

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### COMPETING INTERESTS

The authors declare that they have no competing interests.

### AUTHORS’ CONTRIBUTIONS

The literature review was conducted by M.L., M.v.L. and E.N. Study design and methods were developed by M.L., M.v.L., E.N., B.T.B., E.S., A.J., J.v.O. and T.K. Data analysis was done by M.L., M.v.L., E.N. and J.v.O. Data interpretation was done by M.L., M.v.L., E.N., B.T.B., Z.T., E.S., A.J., A.A., T.K. and J.v.O. Writing was completed by M.L., M.v.L., E.N. and J.v.O. All authors reviewed the final manuscript for submission.

### ACKNOWLEDGEMENTS

We acknowledge the following individuals for their contributions to this manuscript: Drs. Marie Louise Newell and Catherine Yang.

### FUNDING

This project has been supported by the President’s Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (CDC) under the terms of cooperative agreement U2GGH000721 and they had no direct role in study design, implementation, analysis or preparation/submission of this manuscript. The author acknowledges full access to all the data.
and final responsibility for submission. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

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