Uptake and performance of prevention of mother-to-child transmission and early infant diagnosis in pregnant HIV-infected women and their exposed infants at seven health centres in Addis Ababa, Ethiopia

Marshet Girma1,2, Rahel Wendaferash3, Hailu Shibru4, Yemane Berhane1, Michael Hoelscher2,5,6 and Arne Kroidl5,6

1 Addis Continental Institute of Public Health, Addis Ababa, Ethiopia
2 Center for International Health, University of Munich, Munich, Germany
3 Sarris Health Centre, Addis Ababa, Ethiopia
4 Kolfe Health Centre, Addis Ababa, Ethiopia
5 Division of Infectious Diseases and Tropical Medicine, University of Munich, Munich, Germany
6 German Centre for Infection Research, Munich, Germany

Abstract

OBJECTIVE To assess the uptake of WHO-recommended PMTCT procedures in Ethiopia’s health services.

METHODS Prospective observational study of HIV-positive pregnant mothers and their newborns attending PMTCT services at seven health centres in Addis Ababa. Women were recruited during antenatal care and followed up with their newborns at delivery, Day 6 and Week 6 post-partum. Retention to PMTCT procedures, self-reported antiretroviral treatment (ART) adherence and HIV infant outcome were assessed. Turnaround times of HIV early infant diagnosis (EID) procedures were extracted from health registers.

RESULTS Of 494 women enrolled, 4.9% did not complete PMTCT procedures due to active denial or loss to follow-up. HIV was first diagnosed in 223 (45.1%) and ART initiated in 321 (65.0%) women during pregnancy. ART was initiated in a median of 1.3 weeks (IQR 0–4.3) after HIV diagnosis. Poor self-reported treatment adherence was higher post-partum than during pregnancy (12.5% vs. 7.0%, P = 0.002) and significantly associated with divorced/separated marital status (RR 2.2, 95% CI 1.3–3.8), low family income (RR 2.1, 95% CI 1.1–4.1), low CD4 count (RR 1.7, 95% CI 1.0–3.0) and ART initiation during delivery (RR 2.5, 95% CI 1.1–5.6). Of 435 infants born alive, 98.6% received nevirapine prophylaxis. The mother-to-child HIV transmission rate was 0.7% after a median of 6.7 weeks (IQR 6.4–10.4), but EID results were received for only 46.6% within 3 months of birth.

CONCLUSION High retention in PMTCT services, triple maternal ART and high infant nevirapine prophylaxis coverage were associated with low mother-to-child HIV transmission. Declining post-partum ART adherence and challenges of EID linkage require attention.

KEYWORDS PMTCT, antiretroviral treatment adherence, HIV early infant diagnosis, mother-to-child HIV transmission rate, Ethiopia

Introduction

The 2011 Global Plan towards the elimination of new HIV infections among children and keeping mothers alive aimed at reducing new childhood infections by 90% and HIV-related maternal death by 50% by 2015 [1]. Antiretroviral treatment (ART) in HIV-positive pregnant and breastfeeding women in Africa can reduce HIV transmission to below 5% [2]; however, uptake of HIV testing and counselling, uptake of ART, treatment adherence and retention in care and uptake of early infant diagnosis (EID) for HIV-exposed infants remain major challenges. Within the UNAIDS 90-90-90 agenda (90% of people living with HIV know their HIV status, 90% of HIV-infected patients receive treatment, 90% of patients on treatment have a suppressed viral load), these
key elements are targeted [3]. Based on the complexity of previous PMTCT regimens (Option A and B [4]), current guidelines recommend Option B+, which includes immediate and lifelong triple ART irrespective of clinical stage or CD4 cell count for all HIV-infected pregnant and breastfeeding women [5]. This approach was implemented into the Ethiopian National Guidelines in 2013, associated with a National Strategic Plan of Elimination of Mother to Child Transmission of HIV (eMTCT) [6].

Data from the latest 2014 Ethiopian antenatal sentinel surveillance indicated that the HIV prevalence among pregnant women had declined in urban areas from 14.3% in 2001 to 3.9% in 2014, and in rural areas from 4.1% in 2003 to 1.4% in 2014 [7, 8]. The total number of health facilities providing PMTCT services had increased to 2150 in 2013, and the antiretroviral treatment coverage for HIV-positive women was 81% [1, 7, 8]. Single-dose nevirapine (NVP) prophylaxis in HIV-exposed neonates reduces mother-to-child transmission rates and should therefore be taken by infants at least until Week 4 after birth [4, 5]. In HIV-infected infants, the disease progresses rapidly, and without access to treatment mortality approaches 50% at 1 year [9, 10]. EID has improved enrolment in care and contributed to improved outcomes for many children with HIV; however, only 42% of HIV-exposed infants receive a diagnostic test within 2 months of birth, and only 49% of children living with HIV are receiving ART [1–3]. HIV EID based on qualitative HIV-DNA analysis from dry blood spots (DBS) should be collected 4–6 weeks after birth [11]. In African countries, this analysis is performed in centralised laboratories, implicating a cascade of error-prone linkage procedures such as sample transfers to the laboratories, turnaround time for analysis, result reporting to the health facilities, result dissemination to the infant’s care taker and linkage to care and treatment.

Previous Ethiopian studies have investigated adherence to recommended PMTCT and EID procedures in different settings [12–17], but more recent data are needed. We therefore designed a prospective cohort study in urban Addis Ababa to evaluate the uptake and performance of recommended procedures within the maternal and infant PMTCT and EID cascade.

Methods
Study design and settings
In this prospective cohort study, we evaluated retention in care, uptake of maternal antiretroviral PMTCT regimens and adherence, uptake of infant nevirapine prophylaxis and adherence, uptake of and linkage to HIV EID procedures, and resulting neonatal HIV transmission rates. The study was conducted at seven Ethiopian Ministry-affiliated primary health centres (Bole, Kirkos, Gulele, Kolfe, Sarris, Mesholekya and Sheromeda Health Centres) that provide PMTCT and obstetric services in urban Addis Ababa. Health centres were chosen from high catchment areas and distributed across Addis Ababa. The study was conducted by trained health centre-employed nurses, midwives and mother’s support groups for tracing purposes, including two research nurses who assisted in study procedures. PMTCT procedures were performed according to National Guidelines for PMTCT of HIV in Ethiopia [18], which were revised in early 2013 when the Ethiopian government launched Option B+ [6].

Study population
HIV-infected pregnant women aged 18 years or older were contacted during antenatal care (ANC) and eligible for study participation if HIV infection was confirmed either by national HIV testing algorithm or documented medical charts. Women were excluded if there was evidence for mental or physical incapacity. All women received written and oral study information and were required to give written informed consent for themselves and their infants before any study procedures.

Study procedures
Participating women and infants were followed up at the time of delivery, at Day 6 and at Week 6 post-partum following national recommendations for post-natal care and PMTCT. During ANC, women’s characteristics and sociodemographic data were gathered through a study-tailored structured questionnaire that included participants’ tracing information. HIV status and antiretroviral information were obtained either from patient’s blue cards or extracted from hospital charts. Data collected during delivery comprised date and type of delivery, infant outcome (live-born, stillbirth) and gender. During delivery, at Day 6 and Week 6, the maternal ART status was revised and maternal adherence to antiretroviral treatment was assessed using a self-administered questionnaire. The five-item questionnaire included (i) a 4-day recall asking for numbers of skipped doses (never, 1, 2, 3 or 4 skipped doses), (ii) a 1-month recall of voluntary treatment interruptions (never, <1 weeks, 1–2 weeks, more than 2 weeks), (iii) an ordinal question of skipped doses, (iv) shifted doses more than 2 h over the last month (never, rarely, often) and (v) a question about...
following prescription over the past month (totally followed, generally followed, often modified, almost never followed prescription or interrupted treatment). Infant’s assessment included uptake of NVP prophylaxis and adherence, using an adapted five-item questionnaire on difficulties in administering infant prophylaxis completed at Day 6 and Week 6 post-partum. Collection dates of infant DBS, receipt dates of EID results and outcome were extracted from the health centre DBS-EID registers. Samples were transferred to the centralised Addis Ababa Administration Health Bureau, Health Research Laboratory Service for qualitative HIV-DNA assessments for EID.

For women/infants who did not attend study visits, tracing information was sought focused on continuation of PMTCT procedures and infant outcome. Tracing information was included into the outcome analysis if available.

Data collection and statistical analysis
Clinical and laboratory data were recorded in study-specific case report forms and entered into a study-tailored database, which was programmed in Epi Info (CDC Atlanta, Version 3.5.3). Descriptive statistics were reported for maternal baseline characteristics, HIV and ART-associated information, infant outcome, infant prophylactic treatment and EID information. Treatment adherence was graded as good if all adherence questioners indicated optimal compliance (no interruption, never shifted or skipped doses, totally followed prescription); moderate if doses were once or rarely skipped or shifted, or prescriptions were generally followed; poor if doses were skipped or shifted more than once or often, or prescriptions were often modified or ignored. Adherence grades were assessed for mothers and infant for each time-point (delivery, Day 6 and Week 6). Combined post-delivery or overall adherence was summarised, and discrepant adherence grades by different time-points were combined based on the worst case for adjacent grades (poor + moderate = poor) or using the middle value (poor + good = medium). Comparison of treatment adherence before and after delivery was performed using McNemar’s exact test. Study site-adjusted Poisson regression indicating risk ratios (RR) with robust variance estimates was used to analyse socio-demographic and HIV-related risk factors associated with poor antiretroviral treatment adherence. For all statistical tests, an alpha level of <0.05 was used to define significance. All statistical analyses were performed using Stata statistics software (version 14, StataCorp, College Station, TX, USA).

Ethical considerations
This study was approved by the Ethical Clearance Committee of the Addis Ababa City Administration Institutional Health Bureau, the Ethical Review Board of the Addis Continental Institute of Public Health, and the Ethics Committee at the University of Munich in Germany. Participation was free and voluntary, and the study was conducted according to the ethical principles of the Helsinki Declaration.

Results
Between October 2012 and July 2015, 494 HIV-infected pregnant women were enrolled into the study. Woman’s study site affiliation, baseline demographic, socioeconomic, educational, occupational and HIV status characteristics are shown in Table 1. In brief, the median age was 28 years; the majority of women were married and Orthodox Christians, had primary or secondary school degrees, were house wives or private employees, with a median monthly family income of 1000 Ethiopian Birr (around 47 USD). The median CD4 count was 387 cells/µl; 42.1% had a last CD4-count <350 cells/µl. HIV infection was known before pregnancy in 263 (53.2%) women, and HIV was first diagnosed in 223 (45.1%) women during this pregnancy. Very late HIV diagnosis <4 weeks before delivery or at the time of delivery was made in 6 (2.7%) and 3 (1.4%) women, respectively (Figure 2a).

After enrolment, 17 (3.4%) women decided to continue PMTCT and obstetric services outside the study sites, 7 (1.4%) were transferred to higher-level health facilities due to obstetric problems, and 7 (1.4%) did not continue with study procedures due to abortion or foetal death before the date of delivery. Another two women decided to not continue with PMTCT procedures and 19 were lost to follow up for unknown reasons before delivery (Figure 1). Of the remaining 442 women who were followed up during delivery, 19 mother/infant pairs dropped out of study procedures until Week 6 post-partum either because they continued post-natal services at other health facilities (N = 5), or because of still birth (N = 6), early infant death (N = 3), maternal death (N = 1) or unwillingness (N = 3). In total, 24 (4.9%) women chose not to complete PMTCT services or were lost to follow-up.

Maternal ART initiation and adherence
Antiretroviral treatment was initiated during or after pregnancy in 321 women, of whom 94 (29.3%) were
known to be HIV-positive before the current pregnancy but still ART naïve; 220 (68.5%) women were HIV diagnosed during this pregnancy, and for seven women, the date of HIV diagnosis was not known. Most women received a fixed-dose combination of tenofovir, lamivudine and efavirenz, and 37 women received zidovudine monotherapy according to Option A guidelines. The median time of ART initiation before delivery in women starting treatment during pregnancy was 17.4 weeks (IQR 11.7–23.9). Antiretroviral PMTCT coverage was critical in 19 (5.9%) women who initiated ART <4 weeks, and suboptimal in 56 (17.4%) women who initiated ART 4–12 weeks before delivery (Figure 2b). Very late or late ART initiation in these 75 women was due to either late HIV diagnosis in 46 (61.3%), or due to

Table 1 (Continued)

| Variable                                      | Total population | N = 494 |
|-----------------------------------------------|------------------|---------|
| 3rd trimester                                 | 250 (50.6)       |         |
| Time of first HIV diagnosis                   |                  |         |
| Before current pregnancy                      | 263 (53.2)       |         |
| During current pregnancy                      | 223 (45.1)       |         |
| Not known                                     | 8 (1.6)          |         |
| Start of antiretroviral therapy               |                  |         |
| Before current pregnancy                      | 166 (33.6)       |         |
| During/after current pregnancy                | 321 (65.0)       |         |
| Not known                                     | 7 (1.4)          |         |
| WHO stage                                     |                  |         |
| Stage 1/2                                     | 450 (91.1)       |         |
| Stage 3/4                                     | 44 (8.9)         |         |
| Last CD4 count (cells/μl)                     |                  |         |
| Median (IQR)                                  | 387 (261–536)    |         |
| <200 cells/μl                                 | 73 (14.8)        |         |
| 200 to <350 cells/μl                          | 135 (27.3)       |         |
| ≥350 cells/μl                                 | 268 (54.3)       |         |
| Missing data                                  | 18 (3.6)         |         |

Values are provided for numbers (%), or medians (IQR) for continuous variables.

*1 US Dollar = 21.55 Ethiopian Birr (1000 Ethiopian Birr = 46.41 USD).

†Tenofovir (TDF), lamivudine (3TC), zidovudine (ZDV), nevirapine (NVP), efavirenz (EFV).
delayed ART initiation despite known HIV diagnosis in 29 (38.7%) cases. In newly HIV-diagnosed women, the median time between HIV diagnosis and start of ART (test and treat) was 1.3 weeks (IQR 0–4.3). In 25.9%, ART was initiated on the day of HIV diagnosis, cumulatively within 1 week in 46.4%, and within 1 month in 74.1% (Figure 2c).

Overall self-reported antiretroviral treatment adherence was good in 41.3% and poor in 17.3%, and adherence was comparable between women who had started ART during pregnancy or were on ART already before pregnancy (Table 2). Treatment adherence was significantly better before delivery than afterwards (good adherence: 60.8% vs. 50.5%, P ≤ 0.001; poor adherence: 7.0% vs. 12.5%, P = 0.002). Socio-demographic factors significantly associated with poor self-reported treatment adherence were as follows: divorce, separation or widowhood (RR 2.2, 95% CI 1.3–3.8, P = 0.004), and low family income (RR 2.1, 95% CI 1.1–4.1, P = 0.027), whereas age, religion, ethnicity, education, occupation, HIV diagnosis or ART initiation before or during pregnancy were not associated with poor adherence (Table 3). In women starting ART during pregnancy, poor treatment adherence was significantly associated with CD4 counts <200 cells/μl (RR 1.7, 95% CI 1.0–3.0, P = 0.049) and ART initiation during delivery (RR 2.5, 95% CI 1.1–5.6,
P = 0.028). No association was seen with WHO stages or ART initiation within 1 week after HIV diagnosis.

### Infant outcome and EID linkage procedure

Infant outcome information, either directly obtained during study visits or through active tracing, indicated that 435 (88.1%) infants were born alive (50.1% males, 9.4% caesarean sections), 10 (2.0%) were stillbirths, 7 (1.4%) were abortions or early intrauterine foetal deaths, and for 42 (8.5%) infants, no outcome information was obtainable. Four infants died during the post-natal period because of respiratory distress, pneumonia or for unknown reasons; for none of these infants, HIV infection information was collected. Nevirapine prophylaxis was initiated in 98.6% of infants born alive, and in two cases, prophylaxis was not initiated due to early infant death or mother’s refusal, and in four infants previously

#### Table 2  Treatment adherence (overall, before and after delivery) in HIV-infected pregnant women for the total population and stratified by ART initiation before or during/after the current pregnancy

| ART adherence until delivery | ART adherence after delivery until Week 6 | Overall ART adherence |
|-----------------------------|----------------------------------------|-----------------------|
| ART initiation              | ART initiation                         | Overall ART adherence |
| during/after pregnancy      | during pregnancy                       | during pregnancy      |
| N = 494                    | N = 321*                               | N = 166*              |
| Good                       | Good                                   | Good                  |
| 296 (60.8)                 | 246 (50.5)                             | 201 (41.3)            |
| Moderate                   | Moderate                               | 138 (28.3)            |
| 92 (18.9)                  | 116 (23.8)                             | 84 (17.3)             |
| Poor                       | Poor                                   | 64 (13.1)             |
| 34 (7.0)                   | 61 (12.5)                              | 39 (12.2)             |
| Missing information        | Missing information                    | 64 (13.1)             |
| 65 (13.3)                  | 64 (13.1)                              | 39 (12.2)             |

#### Table 3  Demographic, socioeconomic, HIV status and antiretroviral risk factors associated with overall poor antiretroviral treatment adherence adjusted by study sites

| Variable                          | n/N (%)     | RR (95% CI) | P-value |
|-----------------------------------|-------------|-------------|---------|
| Age groups                        |             |             |         |
| 18–24 years                       | 24/93 (25.8) | 1           | -       |
| 25–29 years                       | 32/174 (18.4)| 0.7 (0.4–1.1)| 0.156   |
| ≥30 years                         | 27/156 (17.3)| 0.7 (0.4–1.1)| 0.112   |
| Marital status                    |             |             |         |
| Married, committed, cohabitating  | 69/355 (19.4)| 1           | -       |
| Single                            | 5/47 (10.6)  | 0.5 (0.2–1.3)| 0.167   |
| Divorced, separated, widowed      | 9/21 (42.9)  | 2.2 (1.3–3.8)| 0.004   |
| Religion                          |             |             |         |
| Orthodox Christian                | 73/274 (21.0)| 1           | -       |
| Muslim                            | 3/40 (7.5)   | 0.4 (0.1–1.1)| 0.066   |
| Protestant or Catholic Christian  | 7/36 (19.4)  | 0.9 (0.5–1.9)| 0.822   |
| Ethnicity                         |             |             |         |
| Oromo                             | 28/119 (23.5)| 1           | -       |
| Amhara                            | 42/201 (20.9)| 0.9 (0.6–1.4)| 0.639   |
| Gurage                            | 7/52 (13.5)  | 0.6 (0.3–1.2)| 0.150   |
| Tigre                             | 4/32 (12.5)  | 0.5 (0.2–1.4)| 0.205   |
| Wolyata                           | 0/9 (0)      |             |         |
| Other                             | 2/8 (20)     | 0.8 (0.2–3.1)| 0.804   |
| Education                         |             |             |         |
| (post) Secondary                  |             |             |         |
| Primary                           | 16/82 (19.5) | 1.0 (0.6–1.6)| 0.880   |
| No school degree                  | 11/68 (16.2)| 0.8 (0.4–1.4)| 0.449   |
| Occupation                        |             |             |         |
| House Wife                        |             |             |         |
| 44/212 (20.8)                     | 1           | -           |         |
| Private employee                  |             |             |         |
| 12/90 (14.4)                      | 0.7 (0.4–1.2)| 0.212     |         |
| Daily labourer                    |             |             |         |
| 6/40 (15.0)                       | 0.7 (0.3–1.6)| 0.409     |         |
| Government employee               |             |             |         |
| 8/30 (26.7)                       | 1.3 (0.7–2.5)| 0.434     |         |
| House maid                        |             |             |         |
| 4/29 (13.8)                       | 0.7 (0.3–1.7)| 0.399     |         |
| Commercial sex worker             |             |             |         |
| 2/7 (28.6)                        | 1.4 (0.4–4.6)| 0.609     |         |
| Other                             |             |             |         |
| 6/15 (40.0)                       | 1.9 (1.0–3.8)| 0.064     |         |
| Family income                     |             |             |         |
| >2500                             |             |             |         |
| 10/76 (13.2)                      | 1           | -           |         |
| 1501–2500                         |             |             |         |
| 19/80 (23.8)                      | 1.8 (0.9–3.6)| 0.098     |         |
| 501–1500                          |             |             |         |
| 25/162 (15.4)                     | 1.2 (0.6–2.3)| 0.638     |         |
| 0–500                             |             |             |         |
| 29/105 (27.6)                     | 2.1 (1.1–4.1)| 0.027     |         |
| HIV diagnosis                     |             |             |         |
| During pregnancy                  |             |             |         |
| 37/195 (19.0)                     | 1           | -           |         |
| Before pregnancy                  |             |             |         |
| 44/224 (19.6)                     | 1.0 (0.7–1.5)| 0.863     |         |
| ART initiation                    |             |             |         |
| During pregnancy                  |             |             |         |
| 55/281 (19.6)                     | 1           | -           |         |

Values are provided for numbers (%).

*N = 7 women missing information on ART initiation.

†Overall adherence includes any adherence information provided, either before and after delivery, or only before or only after delivery.
referred to other health facilities, no information was obtainable. Self-reported adherence to NVP prophylaxis was good in the majority of patients; however, adherence reported at Week 6 was better than adherence reported at Day 6 (good adherence: 80.9% vs. 76.6%, \( P = 0.028 \); poor adherence: 3% vs. 7.4%, \( P = 0.003 \)) (Table 4).

Dry blood spots for EID was collected after a medium duration of 6.7 weeks (IQR 6.4–10.4) after birth. DBS collection categorised by week after delivery (Figure 3a) indicated that only 12.2% had blood collected within the recommended period of 4–6 weeks post-partum, 68.2% cumulatively by Week 8 and 77.5% by Week 12 post-partum. Eighty-three (19.1%) infants had DBS collected later than 12 weeks post-partum, some of those more than 1 year after delivery. The turnaround time between DBS collection and receipt of EID results at the health centre was a median 4.1 weeks (IQR 2.3–4.7). Turnaround times by week categories (Figure 3b) indicated that cumulatively health centres had received EID results for 41.4% of infants by Week 4, for 76.3% by Week 8 and for 7.6% later than 8 weeks after DBS collection. The turnaround time between birth and receipt of EID was a median 11.3 weeks (IQR 10.1–16.4). HIV results were available for 4.8% of infants after 8 weeks, for 46.7% cumulatively within 12 weeks and for 71.5% within 24 weeks; 54 (12.4%) infants’ results were available after 24 weeks, some of these even after 1 year (Figure 3c). Of the 424 infants with available EID results, only two (0.5%) were HIV-DNA reactive. In both cases, mothers received triple ART and infants received NVP prophylaxis, and from them, DBS samples were collected around Week 7 and EID results were available around Week 9 post-partum. The third HIV-infected infant was born to a mother who terminated PMTCT during pregnancy, had home delivery and later DBS-EID procedures performed elsewhere with results available following tracing information. Therefore, the transmission rate in infants born alive with available HIV infant outcome

### Table 3 (Continued)

| Variable | Poor ART adherence adjusted by study site |
|----------|------------------------------------------|
|          | n/N (%) | RR (95% CI) | P-value |
| Before pregnancy | 28/141 (19.9) | 1.0 (0.7–1.5) | 0.934 |
| Only women starting ART during pregnancy | | | |
| WHO stage | | | |
| Stage 1/2 | 53/269 (19.7) | 1 | – |
| Stage 3/4 | 2/12 (16.7) | 0.9 (0.2–3.2) | 0.848 |
| CD4 count | | | |
| ≥350 cells/μl | 28/153 (18.3) | 1 | – |
| 200 to <350 cells/μl | 10/77 (13.0) | 0.7 (0.4–1.4) | 0.313 |
| <200 cells/μl | 14/44 (31.8) | 1 (1.0–3.0) | 0.049 |
| ART start before delivery | | | |
| >12 weeks | 35/209 (16.8) | 1 | – |
| 8–12 weeks | 7/27 (25.9) | 1.6 (0.8–3.2) | 0.205 |
| 4–8 weeks | 6/27 (22.2) | 1.3 (0.6–2.8) | 0.501 |
| <4 weeks | 3/8 (37.5) | 2.2 (0.9–5.6) | 0.097 |
| At/after delivery | 4/10 (40.0) | 2.5 (1.1–5.6) | 0.028 |
| ART initiation after HIV diagnosis | | | |
| ≥1 week after | 38/188 (20.2) | 1 | – |
| HIV diagnosis | | | |
| <1 week after | 15/89 (16.9) | 0.8 (0.5–1.4) | 0.512 |

Values are provided in numbers of cases (n)/numbers of participants analysed (N) and percentage (%). RR = risk ratio (95% exact/Clopper-Pearson confidence interval) and P-values were calculated using study-site-adjusted Poisson regression analysis; significant values are highlighted in bold.

### Table 4 Infant outcome, nevirapine (NVP) prophylaxis and adherence in infants born alive. Data include tracing information for infants who continued PMTCT procedures outside the study sites

| Variable | Life-born infants (N = 435) |
|----------|----------------------------|
| Gender | | |
| Female | 214 (48.7) |
| Male | 218 (50.1) |
| No information | 5 (1.2) |
| Type of delivery | | |
| Spontaneous vaginal delivery | 388 (89.2) |
| Assisted vaginal delivery (vacuum/forceps) | 1 (0.2) |
| Caesarean section | 41 (9.4) |
| No information | 5 (1.2) |
| NVP prophylaxis | | |
| Started | 431 (98.6) |
| Not started | 2 (0.5) |
| Missing information | 4 (0.9) |
| NVP adherence until Day 6 post-partum | | |
| Good | 333 (76.6) |
| Moderate | 57 (13.1) |
| Poor | 32 (7.4) |
| No information | 4 (0.9) |
| NVP adherence between Day 6 and Week 6 post-partum | | |
| Good | 352 (80.9) |
| Moderate | 53 (12.2) |
| Poor | 13 (3.0) |
| No information | 17 (3.9) |
| Infant outcome | | |
| Not HIV infected | 428 (98.4) |
| HIV infected | 3 (0.7) |
| Early infant death | 4 (0.9) |

Values are provided for numbers (%).
Information was 0.7% (3/431 infants). For four infants who died within the 6 weeks post-partum period, no HIV results were available; a possible HIV-related cause of infant death could not be excluded. The transmission rate in infants of mothers who received adequate PMTCT coverage was 0.5% (2/429 infants), two mothers did either not comply with PMTCT procedures or were lost to follow-up for unknown reasons which resulted in one infant HIV transmission. We followed up 422 infants who were HIV negative by Week 6 for 18 months and none of them were HIV seropositive.

**Discussion**

In our prospective study of HIV-infected pregnant women and their newborn infants, we observed a low HIV mother-to-child HIV transmission rate of 0.7% after a median of 6.7 weeks indicating high effectiveness of the current PMTCT procedures. The transmission rate was 0.5% when accounting for mothers who received adequate PMTCT coverage only. For a great number of infants, we were able to achieve HIV outcome results at 18 months which indicated that no infant was HIV-infected during the breastfeeding period. Previous Ethiopian studies have reported transmission rates of 14.3% in 2006, 14.9% in 2007 [19] and between 8.2% and 9.5% in 2009 [17]. Further retrospective data from the Gondar University Referral Hospital indicated 10% transmission between 2005 and 2011 [20], and 15.7% between 2005 and 2013 at Dil Chora Referral Hospital [21]. Our data therefore reflect the beneficial impact of the latest recommendations on maternal and infant antiretroviral prevention in Ethiopia, namely the introduction of maternal triple ART regimens. Data from the PROMISE study in India and several African countries reported similar transmission rates of 0.5% and 0.6% among women receiving triple ART [21].

The uptake of PMTCT procedures in our study was very good with a loss of follow-up rate of 4.9%, which is less than reported in other studies [22–25]. The majority of women in our study were HIV diagnosed and started ART during pregnancy within a median duration of 1.3 weeks between HIV diagnosis and ART initiation. The immediate initiation or ART at the time of HIV diagnosis, as recommended within the Option B+ procedures, is controversially debated as there is concern on sustained treatment adherence. In fact, defaulting from treatment has been reported to be higher in women starting on Option B+ as than in those who were already on ART based on clinical and immunological criteria [26–28]. In our analysis, we did not observe differences in self-reported treatment adherence between women who immediately started ART and those with delayed ART initiation, or between women who started ART during pregnancy and those who were already on ART.

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**Figure 2** (a) Weeks of HIV diagnosis before delivery in N = 223 HIV-infected pregnant women who received first HIV diagnosis during pregnancy; (b) weeks of ART initiation before delivery in N = 321 HIV-infected pregnant women who initiated ART during pregnancy; (c) weeks between HIV diagnosis and ART initiation in N = 220 HIV-infected pregnant women who received first HIV diagnosis during pregnancy and initiated ART during pregnancy.
prior to pregnancy. Late treatment initiation despite known HIV infection in 38.7% of cases could have been avoided by applying test-and-treat procedures.

Self-reported ART adherence in our study indicated a substantial proportion of women admitting poor or moderate treatment adherence. Although this apparently did not lead to high mother-to-child transmission rates, it may raise concern on treatment durability and development of drug resistance as reported in pregnant women from South Africa [29] and Malawi [30]. Evidence for poor post-partum treatment adherence [25] was also seen in our analysis, as the proportion of women with self-reported poor adherence was significantly higher during the post-partum period than before delivery. Poor self-reported adherence was significantly associated with women who started ART very late during the perinatal period, indicating that enforced adherence counselling after delivery is especially needed in these women. Other risk factors associated with poor treatment adherence were low CD4 counts, women who were separated, divorced or widowed, and women with severe financial constraints. Severe economic constraints probably represent the most important social risk factor in our population, translating into lack of transportation money to the health care facilities or lack of time for personal health care instead of generating income. Intervention packages to increase the uptake and adherence to ART in Africa, including enforced patient counselling on HIV surrogate markers such as CD4 counts and strategies to meet economic challenges, are currently investigated in the PopART Study [31].

Infant prophylactic NVP exposure in our study was very good and almost all infants started and completed treatments, likely attributable to the low mother-to-child transmission rate observed. Self-reported adherence to NVP prophylaxis was better after 1 week than in the first 6 days after birth, possibly reflecting initial difficulties with administering the NVP syrup. In contrast, the analysis of EID procedures in our study revealed major challenges. Although the time of infant dry blood sample collection (median 6.7 weeks after birth) and turnaround time of EID results after DBS collection (median 4.1 weeks) was relatively reasonable, only 4.8% of EID results were available within the recommended 2 months after birth, and cumulatively 46.6% within 3 months. In a substantial proportion of cases, EID results were received much later. The fact that that all infants alive received DBS collections and had reported EID results is most probably biased by study-related perseverance. One of the major reasons for deficiencies in EID procedures in our study was a central stock-out of laboratory reagents for HIV-DNA measurements in 2013 which lasted several months. Similar problems are known from other African countries as reflected within the UNAIDS report [1] and recent reviews [23, 24]. Problems related to centralised EID procedures and linkage might be overcome by the introduction of novel point-of-care HIV diagnostic

**Figure 3** Turnaround time of DBS-EID procedures. Proportion of N = 435 infants born alive who received (a) dry blood spots (DBS) collection for early infant HIV diagnosis EID by weeks after delivery, (b) EID results received at health facilities by weeks after DBS collection and (c) EID results at health facilities by weeks after delivery.

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systems as recently recommended by WHO [32], which enable EID procedures directly at the health facilities with turnaround times of <2 h [33].

In conclusion, our study demonstrated low HIV transmission rates from mothers who, for the majority, received triple ART during pregnancy associated with high infant NVP prophylaxis coverage. Limitations for the generalisability of our results are mainly study procedure-related (selection bias leaving out most-at-risk cases who do not reach services, optimised tracing procedures, repeated treatment counselling beyond the usual routine procedures, perseverance in attaining EID results). Efforts to maintain antiretroviral treatment coverage and adherence are especially important during the post-partum period.

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References

1. UNAIDS. 2015 Progress Report on the Global Plan towards the elimination of new HIV infections among children and keeping their mothers alive. (Available from: http://www.unaids.org/sites/default/files/media_asset/JC2774_2015ProgressReport_GlobalPlan_en.pdf) [25 March 2016].

2. UNAIDS. Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, 2014. (Available from: http://www.unaids.org/en/resources/documents/2015/JC2774_2015ProgressReport_GlobalPlan), [25 Mar 2016].

3. UNAIDS. 90-90-90: an ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS, 2014. (Available from: www.unaids.org/en/resources/documents/2017/90-90-90), [5 Apr 2016].

4. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: recommendations for a public health approach, 2010. (Available from: http://apps.who.int/iris/bitstream/10665/75236/1/9789241599818_eng.pdf) [27 March 2016].

5. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, 2013. (Available from: http://www.who.int/hiv/pub/guideline/arv2013/en/) [27 March 2016].

6. Ethiopian Federal Republic Ministry of Health. The national strategic plan of elimination of mother to child transmission of HIV (e-MTCT of HIV), 2013. (Available from: http://www.moh.gov.et/pmtct) [24 March 2016].

7. Central Statistical Agency [Ethiopia]. Ethiopia Mini Demographic and Health Survey 2014. Addis Ababa, Ethiopia. (Available from: http://www.unicef.org/ethiopia/Mini_DHS_2014_Final_Report.pdf) [26 March 2016].

8. Federal HIV/AIDS Prevention and Control Office (FHPACO). Country Progress Report on the HIV Response 2014. Addis Ababa, Ethiopia. (Available from: http://www.unaids.org/sites/default/files/country/documents/ETH注明来源/2014_Country Progress Report.pdf) [26 March 2016].

9. Mphantswe W, Blanckenberg N, Tudor-Williams G et al. High frequency of rapid immunological progression in African infants infected in the era of perinatal HIV prophylaxis. AIDS 2007: 21: 1253–1261.

10. Prendergast A, Mphantswe W, Tudor-Williams G et al. Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. AIDS 2008: 22: 1333–1343.

11. World Health Organization. Antiretroviral therapy of HIV infection in infants and children: towards universal access: recommendations for a public health approach, 2010. (Available from: http://www.who.int/hiv/pub/paediatric/infect_2010/en/) [26 March 2016].

12. Ebh H, Yehyo H, Alemayehu M. Level of adherence and predictors of adherence to the Option B+ PMTCT programme in Tigray, northern Ethiopia. Int J Infect Dis 2015: 33: 123–129.

13. Amberbir A, Woldemichael K, Getachew S et al. Predictors of adherence to antiretroviral therapy among HIV-infected persons: a prospective study in Southwest Ethiopia. BMC Public Health 2008: 8: 265.

14. Tiyou A, Belachew T, Alemseged F et al. Predictors of adherence to antiretroviral therapy among people living with HIV/AIDS in resource-limited setting of southwest Ethiopia. AIDS Res Ther 2010: 7: 39.

15. Tadios Y, Davey G. Antiretroviral treatment adherence and its correlates in Addis Ababa. Ethiop Med J 2006: 44: 237–244.

16. Debito T, Deyno S. Rate and predictors of adherence to antiretroviral therapy among clients on antiretroviral therapy at TEPi health center, south-west Ethiopia. Sci Technol Arts Res J 2014: 3: 93–98.

17. Mirkuzie AH, Hinderaker SG, Sisay MM et al. Current status of medication adherence and infant follow up in the prevention of mother to child HIV transmission programme in Addis Ababa: a cohort study. J Int AIDS Soc 2011: 14: 50.

18. The Federal Republic Ministry of Health. Accelerated plan for scaling prevention of mother to child transmission services in Ethiopia, 2014. (Available from: http://pdf.usaid.gov/pdf_docs/PA00JWM5.pdf) [23 March 2016].
19. Mirkuzie AH, Hinderaker SG, Mørkve O. Promising outcomes of a national programme for the prevention of mother-to-child HIV transmission in Addis Ababa: a retrospective study. *BMC Health Serv Res* 2010: 10: 1–10.
20. Koye DN, Zeleke BM. Mother-to-child transmission of HIV and its predictors among HIV-exposed infants at a PMTCT clinic in northwest Ethiopia. *BMC Public Health*. 2013: 13: 398.
21. Wudineh F, Damtew B. Mother-to-child transmission of HIV infection and its determinants among exposed infants on care and follow-up in Dire Dawa City, Eastern Ethiopia. *AIDS Res Treat* 2016: 2016: 3262746.
22. US National Institute of Health. NIH-sponsored study identifies superior drug regimen for preventing mother-to-child hiv transmission. Press release 17 November 2014. (Available from: http://www.niaid.nih.gov/news/newsreleases/2014/Pages/HIVprevention.aspx) [27 March 2016].
23. Dzangare J, Takarinda KC, Harries AD et al. HIV testing uptake and retention in care of HIV-infected pregnant and breastfeeding women initiated on ‘Option B+’ in rural Zimbabwe. *Trop Med Int Health* 2016: 21: 202–209.
24. Luzuriaga K, Mofenson LM. Challenges in the elimination of pediatric HIV-1 infection. *N Engl J Med* 2016: 374: 761–770.
25. Atanga PN, Ndetai HT, Achidi EA, Meriki HD, Hoelscher M, Kroidl A. Retention in care and reasons for discontinuation of lifelong antiretroviral therapy in a cohort of Cameroonian pregnant and breastfeeding HIV-positive women initiating “Option B+” in the South West Region. *Trop Med Int Health* 2017: 22: 161–170.
26. Kim MH, Ahmed S, Abrams EJ. Paediatric HIV: progress on prevention, treatment and cure. *Curr Pediatr Rep* 2015: 3: 219–229.
27. Haas AD, Tenteni L, Msukwa MT et al. Retention in care during the first 3 years of antiretroviral therapy for women in Malawi’s option B+ programme: an observational cohort study. *Lancet HIV* 2016: 3: e175–e182.
28. Mitiku L, Arefayne M, Mesfin Y et al. Factors associated with loss to follow-up among women in Option B+ PMTCT programme in northeast Ethiopia: a retrospective cohort study. *J Int AIDS Soc* 2016: 19: 20662.
29. Hoffmann CJ, Cohn S, Mashabela F et al. Treatment failure, drug resistance, and CD4 T-cell count decline among postpartum women on antiretroviral therapy in South Africa. *J Acquir Immune Defic Syndr* 2016: 71: 31–37.
30. Mancinelli S, Galluzzo CM, Andreotti M et al. Virological response and drug resistance 1 and 2 years post-partum in HIV-infected women initiated on life-long antiretroviral therapy in Malawi. *AIDS Res Hum Retroviruses* 2016: 32: 737–742.
31. Hayes R, Ayles H, Beyers N et al. HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment – a study protocol for a cluster randomised trial. *Trials* 2014: 15: 57.
32. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2016. (Available from: http://www.who.int/hiv/pub/arv/chapter2.pdf) [25 March 2016].
33. Essajee S, Vojnov L, Penazzato M et al. Reducing mortality in HIV-infected infants and achieving the 90-90-90 target through innovative diagnosis approaches. *J Int AIDS Soc* 2015: 18(Suppl 6): 20299.