The Impact of Maternal Highly Active Antiretroviral Therapy and Short-Course Combination Antiretrovirals for Prevention of Mother-to-Child Transmission on Early Infant Infection Rates at the Mulago National Referral Hospital in Kampala, Uganda, January 2007 to May 2009

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Background: Early HIV infant diagnosis and treatment have been shown to dramatically improve survival in infants. Despite these findings, infants accessing HIV diagnosis and treatment remain low in Uganda. We describe the antiretroviral (ARV) drugs given in the Mulago Hospital prevention of mother-to-child transmission (PMTCT) program from January 2007 to May 2009 and its impact on early infant HIV infection rates.

Methods: Pregnant women identified as HIV infected in the Mulago antenatal clinics received one of the following regimens: short-course ARV prophylaxis plus single-dose nevirapine (sdNVP) in labor, highly active antiretroviral therapy (HAART), or sdNVP if they presented in labor. Infants received sdNVP and zidovudine (ZDV) for 1 week. Infants HIV diagnosis was done from 6 weeks after delivery.

Results: 62.3% of HIV-infected women received combination ARVs, including HAART. Early infection rates were highest among infants with no maternal ARV [36.4; 95% confidence interval (CI): 17.2 to 59.3] or only sdNVP (11.2; 95% CI: 8.1 to 14.8). Similar rates were observed for the group that took short-course ARVs, ZDV/sdNVP (4.6; 95% CI: 3.2 to 6.4), and ZDV/lamivudine/sdNVP (4.9; 95% CI: 3.1 to 7.2) and lowest rates for those that took HAART (1.7: 95% CI: 0.8 to 2.8). Overall infection rate was 5.0% (95% CI: 4.1 to 5.9).

Conclusions: Findings indicate low rates of infant infection for mothers receiving combination ARVs. These findings demonstrate that provision of combination ARV for PMTCT is feasible and effective in busy referral hospital's PMTCT programs in resource-limited settings.

Key Words: HIV, PMTCT, antiretroviral therapy, infant infection rate

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INTRODUCTION

Mother-to-child HIV transmission (MTCT) accounts for more than 90% of pediatric HIV infection.[1] Globally, there were approximately 430,000 new pediatric HIV infections in 2008 and more than 270,000 pediatric deaths attributed to HIV infection, with most of the disease burden in sub-Saharan Africa.[2] After the release of the PACTG 076 trial results in 1994,[3] which established the efficacy of giving zidovudine (ZDV) during pregnancy and at labor and delivery to mothers, followed by 6 weeks of ZDV to newborns, other short-course ZDV trials for MTCT were carried out in the mid-1990s in Thailand and Cote d'Ivoire,[4,5] as well as the single-dose nevirapine (sdNVP) trial in Uganda in the late 1990s.[6,7] These short-course prevention of mother-to-child transmission (PMTCT) trials, which were designed for implementation in midlevel and resource-limited setting, showed significant short-term reduction in MTCT in the clinical trials. Since then, governments and international donors have funded PMTCT programs to provide universal rapid antenatal HIV screening to all pregnant women and to provide antiretroviral (ARV) prophylaxis to those HIV infected who are identified in antenatal and delivery units. Although implementation proceeded rapidly in the United States and Europe and in middle-income countries such as Thailand, translation of PMTCT research findings into practice in resource-limited settings has been much slower. Thus, despite successes in the

United States and Europe to reduce MTCT to less than 2%, PMTCT implementation in resource-limited settings remains extremely challenging. Currently, it is estimated that only 28% of pregnant women in sub-Saharan Africa received an HIV test in 2008 and only 45% of pregnant women living with HIV receive ARV PMTCT interventions.[2] Moreover, antenatal attendance of at least 4 visits as recommended by the WHO is low in sub-Saharan Africa, with health facility deliveries even lower.[8] Therefore, even in settings where facilities are equipped to offer comprehensive PMTCT services including combination ARVs, women may not access these services except sdNVP if they choose to deliver outside the health facility.

The Ministry of Health (MOH) in Uganda has promoted the integration of maternal and child health (MCH) services to include HIV counseling and screening, ARV prophylaxis for all HIV-infected women, antiretroviral treatment (ART) provision for women who meet HIV treatment criteria, and early infant diagnosis for all HIV-exposed infants seen in the postnatal MCH clinics. Despite this initiative, in 2007, only 34% (26,484/78,000) of HIV-infected pregnant women received ARVs for PMTCT in Uganda, and only 33% (115,000/350,000) of Ugandans needing highly active ART (HAART) received it across the 286 ART sites in the country.[9]

Early HIV infant diagnosis and rapid treatment have been shown to dramatically improve survival in infants,[10] and the Uganda MOH recommends treating HIV-infected infants (below 1 year) at the earliest opportunity after diagnosis.[11] The first contact with HIV-exposed infants after delivery is usually the first immunization visit at the 6-week postnatal visit. The current Uganda MOH recommendation is to offer DNA polymerase chain reaction (PCR) testing for all HIV-exposed infants in the postnatal clinics.[11]

The PMTCT program in Mulago, which began in 2000, has expanded from use of sdNVP alone to use of combination ARVs including HAART for women who meet current MOH treatment criteria guidelines. This analysis describes the ARV drugs offered in the Mulago Hospital PMTCT program from January 2007 to May 2009, and the impact of this intervention on early infant HIV infection rates.

METHODS

Program Setting and Population

This was a retrospective and descriptive review of the ARV drugs used in the PMTCT program in the Mulago Hospital in Kampala, Uganda, and the effect on early infant HIV infection. The PMTCT program in the Mulago Hospital operates within 3 antenatal clinics (ANCs), 3 labor and delivery units and 1 postnatal clinic. The PMTCT clients were pregnant women with a positive HIV test result during antenatal or reporting for the first antenatal visit with known HIV-positive serostatus. The women were followed up through delivery and the postnatal period, and the infants were assessed for HIV infection at the first postnatal visit.

Maternal and Infant Laboratory Procedures

Maternal

HIV status among women with unknown status was ascertained using 2 serial rapid HIV antibody tests (Abbott Determine HIV-1/ 2 [Abbott Laboratories, Abbott Park, IL] and STAT-PAK HIV-1/2 [Chembio Diagnostics Inc., NY]). A third rapid test (Uni-Gold HIV, Trinity Biotech Plc, Bray, Ireland) was used as a tiebreaker, in accordance with the MOH HIV testing guidelines.[12] Blood samples for HIV-infected women were further analyzed for CD4 cell counts (by flow cytometry using an FACScalibur machine [Becton, Dickinson and Company, Franklin Lakes, NJ]) from an off-site laboratory and women returned for results after 1 week.

Infant

At the 6-weeks postnatal review (or their first return if later), HIV-exposed infants received HIV-1 DNA PCR tests (Roche Amplicor; Roche Diagnostics, Indianapolis, IN) on whole blood or dry blood spots. Results were received between 2 and 4 weeks. All infants with a positive DNA PCR result at their first postnatal visit between the age of 6 weeks and 3 months were considered HIV infected for this analysis.

Maternal ARV Drugs

A 200 mg sdNVP tablet was offered to all HIV-infected women on the first visit (except those on HAART by their first ANC visit) with instructions to take it at the onset of labor. Depending on the clinical and immunological stages and gestational age, women received one of the following ARV regimens, according to the Uganda MOH guidelines.[13] (1) ZDV 300 mg twice daily from 28 weeks of gestation plus sdNVP at onset of labor if CD4 $\geq$350 cells per cubic millimeter and WHO Clinical Stage I or II, (2) ZDV 300 mg plus lamivudine (3TC) 150 mg twice daily from 33 weeks of gestation, plus sdNVP at onset of labor if CD4 $\geq$350 cells per cubic millimeter and WHO Clinical Stage I or II, (3) HAART if CD4 $<$350 cells per cubic millimeter and/or WHO Clinical Stage III or IV (most women on HAART received ZDV/ 3TC/NVP as first-line treatment combination), and (4) mothers identified as HIV infected in labor, receive only sdNVP (In mid 2007 and before, a CD4 cutoff for HAART was 250 cells per cubic millimeter and from January 2009, mothers who reported in labor received sdNVP and started on ZDV/3TC).

Women who swallowed sdNVP in labour were also given ZDV and 3TC for one week after delivery, to counter against resistance. HIV exposed newborns received sdNVP plus 1 week of ZDV (2 mg/kilogram body weight).

Follow-up of Women and Enrollment into Long-Term Care

The women were given additional counseling and support for ARV prophylaxis or HAART. Those who were not part of another HIV care program were enrolled into the Mulago PMTCT follow-up clinic for long-term HIV care, and demographic information, including maternal age, marital status, employment status, and education level, was collected for only this group of women at the time of enrollment. Women were strongly encouraged to deliver at the Mulago Hospital and to return with the infants for 6-week postnatal follow-up visit. Additional strategies to get mothers to return to the hospital included use of "peer" mothers, telephone reminders (50% had telephone contacts), home visits for the

women on HAART, treatment supporters for reminder of clinic visits and medication, and psychosocial support meetings by counselors and peer mothers. Additional staffs were recruited to boost the existing hospital staff in the sections of counseling, laboratory, and medical office, and periodic training in PMTCT-related fields was done for all key staff in the MCH department.

Statistical Analysis

The maternal and infant characteristics were summarized in tabular displays. Early infant HIV infection rates for overall and by different drug regimens were summarized using percentages. To assess the association between early infection status and different maternal and infant characteristics, a regression analysis using Poisson distribution was done. All bivariate variables found with P value less than 0.2 were entered into a multivariate analysis. Crude and adjusted incident risk ratios (IRR) and the corresponding 95% confidence interval (CI) are reported. All statistical analyses were done using STATA-10 statistical software package (STATACorp LP, 2003, Release 8, College Station, TX).[14]

RESULTS

From January 2007 to May 2009, 75,159 new antenatal attendees were registered at the Mulago Hospital. HIV status was ascertained in 74,952 women (99.7%) through both rapid HIV testing and those who reported in ANC with known HIV status from other health units. Ten percent (7941/74,952) were HIV infected, of whom 96.5% (7665/7941) received ARV drugs, including sdNVP. Sixty percent (4807/7941) of the total HIV-positive women reported back for delivery, of which 59% (2831/4807) were enrolment into long-term care in the Mulago (hence demographic characteristics captured). Less than 50% (2365/4807) of mothers returned their infant to the postnatal clinic at or before 3 months of age but with more than 98% DNA PCR testing among those who were seen (Fig. 1).

Table 1 describes the pregnant women who were enrolled into long-term care and also delivered from the Mulago Hospital (n = 2831), by the maternal ARV regimen. Most were between 20 and 29 years (67.4%), with slightly more women receiving HAART (35.5%) in the 30+ year category. There was no difference in maternal ARV received by marital status, employment status, or education level. Women with low CD4 (<350 cells/mm^3) were more likely to receive HAART (85.8%; $P < 0.0001$) with a median CD4 of 214 cells per cubic millimeter [interquartile range (IQR): 146–282 cells/mm^3] for this group. The overall median gestational age at first antenatal visit was 28 weeks (IQR: 24–32), with women on HAART and ZDV/sdNVP reporting 2 weeks earlier than the other groups (26 weeks; IQR: 22–28).

Among the infants who received an HIV test at or before 3 months of age (n = 2337), 88.2% were less than 2 months of age, with median age of 6.4 weeks (IQR: 6.1–7.1 weeks). There was an equal distribution of infants by sex in each maternal ARV group, and higher women were breastfeeding in the sdNVP (97.8%) and the ZDV/lamivudine/sdNVP groups (96.0%) (Table 2).

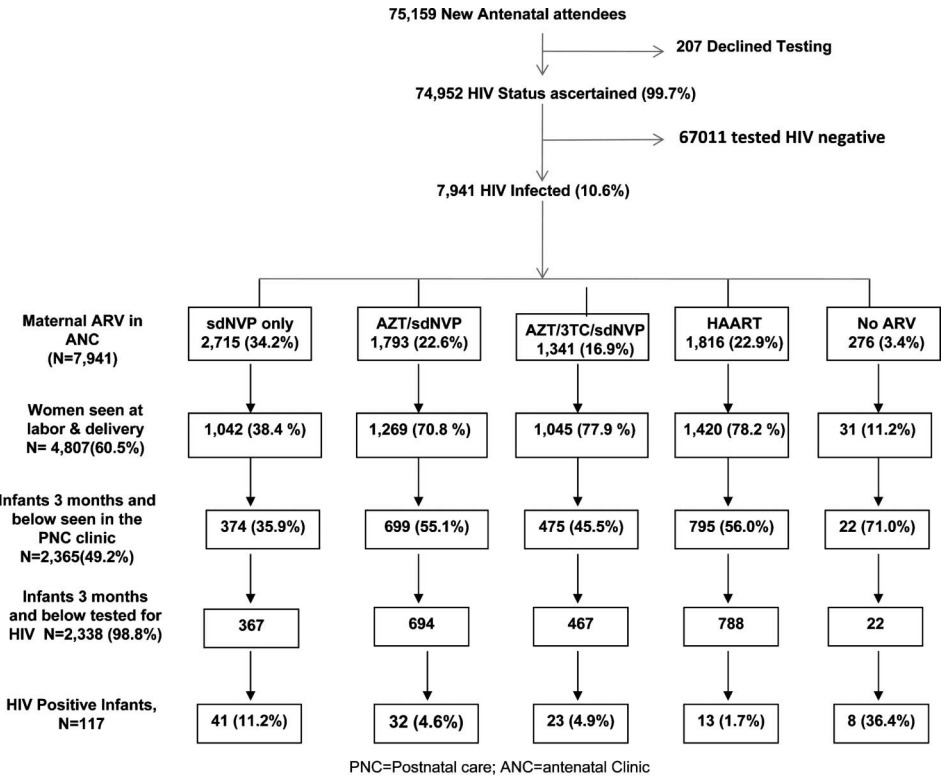

FIGURE 1. Mulago PMTCT Program profile; Jan 2007 to May 2009. PNC, postnatal care.

TABLE 1. Characteristics of HIV-Positive Women Enrolled in Long-Term Care and Delivered in Mulago Hospital from January 2007 to May 2009 (n = 2831).

Characteristics (n = 2831)	No ARV (n = 55)	sdNVP (n = 440)	HAART (n = 533)	ZDV/sdNVP (n = 1032)	ZDV/3TC/sdNVP (n = 771)	P*
Age (years) n (%)						<0.001
<20	6 (10.9)	47 (10.7)	24 (4.5)	102 (9.9)	78 (10.1)	
20–29	33 (60.0)	291 (66.1)	336 (63.0)	711 (68.9)	538 (69.8)	
30+	16 (29.1)	102 (23.2)	173 (35.5)	219 (21.2)	155 (20.1)	
Marital status, n (%)						0.2
Married/consensual	46 (83.6)	350 (79.5)	410 (76.9)	848 (82.2)	595 (77.2)	
Single	7 (12.7)	77 (17.5)	101 (19.0)	148 (14.3)	143 (18.5)	
Widowed/divorced	2 (3.7)	13 (3.0)	22 (4.1)	36 (3.5)	33 (4.3)	
Employment, n (%)						0.4
Employed	22 (40.0)	175 (39.8)	244 (45.8)	436 (42.3)	321 (41.6)	
Not employed	33 (60.0)	265 (60.2)	289 (54.2)	596 (57.7)	450 (58.4)	
Education level, n (%)						0.8
None/primary	30 (54.6)	224 (50.9)	276 (51.8)	508 (49.2)	366 (47.5)	
Secondary	23 (41.8)	186 (42.3)	221 (41.5)	447 (43.3)	351 (45.5)	
Postsecondary	2 (3.6)	30 (6.8)	36 (6.7)	77 (7.5)	54 (7.0)	
CD4 cell/mm^3, n (%)						<0.001
>500	16 (29.1)	156 (33.4)	38 (7.1)	500 (48.5)	396 (51.4)	
350–500	14 (25.5)	87 (19.8)	38 (7.1)	344 (33.3)	249 (32.3)	
<350	25 (45.4)	197 (44.8)	457 (85.8)	188 (18.2)	126 (16.3)	
Median CD4, IQR	371(208–561)	379 (234–592)	214 (146–282)	371 (208–561)	490 (379–663)	<0.001
Median gestation at first ANC visit, IQR	28 (26–30)	28 (26–32)	26 (22–28)	26 (22–28)	28 (24–32)	<0.001

*P values were calculated using χ^2 test for categorical variables, Kruskal–Wallis test for continuous variables.
3TC, lamivudine.

Early infection rates were highest among infants whose mothers received no ARV intervention (36.4; 95% CI: 17.2 to 59.3) followed by infants whose mothers took only sdNVP at the time of labor and delivery (11.2; 95% CI: 8.1 to 14.8), whereas for infants whose mothers took combination ARVs during pregnancy, infection rates were similar: ZDV + sdNVP (4.6; 95% CI: 3.2 to 6.4) and ZDV/3TC + sdNVP (4.9; 95% CI: 3.1 to 7.2), and lowest rates were found among infants whose mothers took HAART during the pregnancy (1.7: 95% CI: 0.8 to 2.8). The overall early infant infection rate was 5.0% (95% CI: 4.1 to 5.9) (Fig 2).

Being widowed was associated with higher risk of infection compared with the married, although not significant (IRR: 1.97; 95% CI: 0.70 to 5.52). Infants whose mothers had postsecondary level of education were more likely to be infected (IRR: 1.73 95% CI: 0.78 to 3.83). The risk of infection increased with reduction in CD4 cell count with IRR of 1.60 (95% CI: 0.86 to 2.95) for the ≥350–500 cell per cubic millimeter group and 1.34 (95% CI: 0.66 to 2.73) for the <350 cell per cubic millimeter group. Use of maternal ARV significantly reduced the risk of infection with IRR 0.23 (95% CI: 0.06 to 0.84) in the sdNVP group, followed by ZDV/sdNVP (IRR: 0.17 95% CI: 0.05 to 0.59) and ZDV/3TC/sdNVP (IRR: 0.19 95% CI: 0.06 to 0.69). The risk of infection was lowest in the group that received HAART (IRR: 0.10 95% CI: 0.03 to 0.38). Male infants were significantly less likely to be infected compared with female infants (IRR: 0.56 95% CI: 0.33 to 0.93) (Table 3).

DISCUSSION

These findings demonstrate that provision of maternal combination ARV drugs during pregnancy can achieve low early infant HIV infection rates in a busy urban hospital in

TABLE 2. Characteristics of Infants Who Received HIV Screening at the First Postnatal Visit at or Before 3 Months of Age in Mulago Hospital from January 2007 to May 2009 (n = 2337)

Infant Characteristics (n = 2337)	No ARV (n = 22)	sdNVP (n = 367)	HAART (n = 788)	ZDV/sdNVP (n = 693)	ZDV/3TC/sdNVP (n = 467)	P
Male sex, n (%)	13 (59.1)	194 (52.8)	425 (53.9)	354 (51.1)	243 (52.0)	0.8
Median age of infant in weeks, IQR	6.3 (6.1–6.7)	6.4 (6.1–7.1)	6.4 (6.1–7.0)	6.3 (6.1–7.0)	6.4 (6.1–7.0)	0.1
Ever/currently Breastfeeding (n = 1659), n (%)*	13 (93.9)	225 (97.8)	497 (89.2)	444 (91.9)	360 (96.0)	<0.001

3TC, lamivudine.

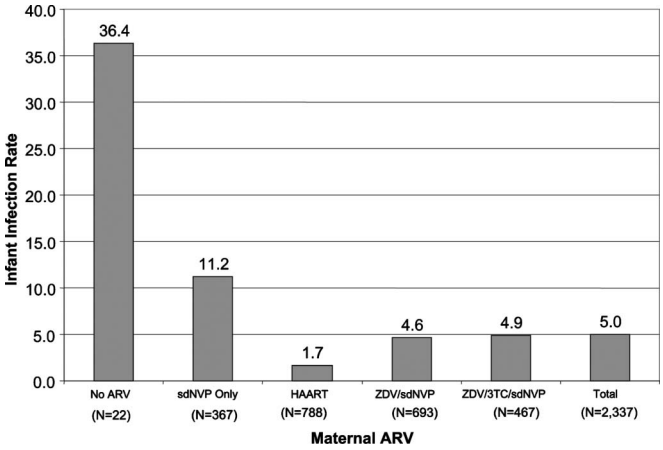

FIGURE 2. Early Infection Rates (≤3 months of age) Among Infants Whose Mothers Received ARV Prophylaxis or HAART in ANC and delivery (N = 2337).

a resource-limited setting. Results showed early infection rates of <5% among infants whose mothers received combination ARVs, compared with rates of 11.2% in those HIV-infected mothers who received only sdNVP at the time of delivery. Women who received HAART for their own care achieved lowest early infant infection rates of <2% despite low maternal CD4 counts.

These findings are highly consistent with results from other observational studies in Africa. Results from the Botswana National PMTCT program showed infection rates of 5% for infants tested at or before 8 weeks of age in a nonbreastfeeding population[15] and 6.5% in 5 predominantly breastfeeding provinces in Zambia among infants 0–6 weeks of age.[16] Data from the KiBS study in Kisumu, Kenya (unpublished, Timothy K. Thomas, MD, January 8, 2010), demonstrated that maternal HAART achieved 6-week transmission rates of 4.2% in a breastfeeding population. Likewise, findings from the DITRAME plus study in Cote d'Ivoire

TABLE 3. Early HIV Infection Rates (≤3 Months of Age) Among Infants Whose Mothers Received ARV Drugs for PMTCT Prophylaxis or Treatment (n = 1328)

Category	n (% Infected)	IRR (95% CI)	Adjusted Incidence Risk Ratio, IRR (95% CI)*
Age (years)			
<20	87 (5.7)	1.0	—
20–29	912 (4.0)	0.69 (0.27 to 1.74)	—
30+	329 (6.1)	1.04 (0.39 to 2.78)	—
Marital status			
Married/consensual	1042 (4.2)	1.0	1.0
Single	233 (5.6)	1.32 (0.71 to 2.45)	1.34 (0.72 to 2.51)
Widowed/divorced	53 (7.6)	1.81 (0.65 to 5.1)	1.97 (0.70 to 5.52)
Employment			
Employed	589 (5.1)	1.0	—
Not employed	739 (4.2)	0.83 (0.50 to 1.37)	—
Education level			
None/primary	633 (4.3)	1.0	1.0
Secondary	582 (4.5)	1.04 (0.61 to 1.79)	1.03 (0.60 to 1.77)
Postsecondary	113 (7.1)	1.69 (0.77 to 3.73)	1.73 (0.78 to 3.83)
CD4 cell/mm^3			
>500	494 (3.9)	1.0	1.0
350–500	356 (6.2)	1.63 (0.88 to 3.01)	1.60 (0.86 to 2.95)
<350	478 (4.2)	1.10 (0.59 to 2.06)	1.34 (0.66 to 2.73)
Maternal ARV			
No ARV	13 (23.1)	1.0	1.0
sdNVP†	181 (11.1)	0.25 (0.07 to 0.9)	0.23 (0.06 to 0.84)
HAART	296 (2.7)	0.11 (0.03 to 0.42)	0.10 (0.03 to 0.38)
ZDV/sdNVP	531 (4.33)	0.18 (0.05 to 0.60)	0.17 (0.05 to 0.59)
ZDV/3TC/sdNVP	307 (5.21)	0.22 (0.06 to 0.75)	0.19 (0.06 to 0.69)
Sex			
Female	641 (5.9)	1.0	1.0
Male	687 (3.4)	0.56 (0.34 to 0.95)	0.56 (0.33 to 0.93)
Infant feeding n (%) (n = 924)			
Never	52 (0)	—	—
Ever/currently breastfeeding	924 (4.7)	—	—

*Rates adjusted for marital status, education level, maternal CD4 cell count, maternal ARV, and sex of the baby.
†CD4 cell cut off for HAART was 250 cell/mm^3 before mid 2007, and from Jan 2009, mothers who reported in labor received sdNVP and started on ZDV and 3TC
3TC, lamivudine.

showed infection rates of 6.5% with ZDV/sdNVP and 4.7% with ZDV/3TC/sdNVP at 6 weeks.[17] Results using a 2-tiered approach of giving HAART and short-course AZT or AZT/3TC plus sdNVP demonstrate low and similar 12-month postnatal transmission rates of 3.8% in the HAART group and 5.7% in the short-course ARV, with overlapping confidence limits with either strategy.[18]

More than 90% of the women in our PMTCT program breastfed. Following the current WHO PMTCT recommendation,[19] there is urgent need to adopt these guidelines in national PMTCT programs to reduce the infection while continuing to breastfeed. Findings from the Breastfeeding, Antiretrovirals, and Nutrition study (BAN) study in Malawi showed that giving maternal HAART or extended NVP for the baby greatly reduced HIV infection during breastfeeding.[20] In another study done in Burkina Faso, infants who continued to breastfeed while their mothers were on HAART still had lower infection rate at 18 months compared with women who took only short-course ARVs.[21] These findings and the WHO recommendations would require early maternal HIV testing in ANC and initiation of appropriate antepartum ARV drugs with rigorous follow-up of both the mother and the infant. With a median gestation age for first ANC booking of 28 weeks observed in our program, interventions to get women earlier will be needed.

This data showing high uptake of maternal rapid HIV screening, offering combination ARV drugs and low transmission rates, confirms that translation of trial findings into PTMCT practice is feasible in resource-limited settings *if* adequate resources, including staffing and training, are made available.[22] Less than 50% of mothers returned their infants to the postnatal clinic, further necessitating innovative strategies that encourage HIV-infected women to return after delivery for their own care and infant HIV testing. Strategies beyond peer support in the antenatal clinics and use of mobile phone reminders need to be studied. One strategy that will be looked at is the development of a point of care infant HIV PCR results (Rapid HIV PCR test), so mothers can learn their infants HIV status the same day they come to the clinic.

The Mulago Hospital PMTCT program demonstrates what can be achieved with adequate funding and on-going training to ensure maintenance of well-trained staff. In many resource-limited settings, MCH services are under funded with inadequate numbers of trained health care workers to carry out the MCH and PMTCT activities. Integrating PMTCT programs successfully within MCH requires a commitment at both the local and national levels to ensure that adequate funding support is given for both MCH and PMTCT activities. In the long run, providing this support will be highly cost effective in preventing both MTCT and increasing the uptake of childhood immunizations, growth monitoring, and other MCH services that improve overall infant survival.

Limitations of this analysis include the high loss to follow-up before delivery and postnatal care, and the data available are limited to clients who enrolled in the Mulago PMTCT follow-up program. Early infant infection rates (<3 months of age) were presented but not later infection rates among those infants who continued breastfeeding. Information on breastfeeding was not fully presented due to missing data. Despite these limitations, the early infant infection rates are consistent with other PMTCT programs and trials. The large number of clients in the PMTCT program provided sufficient power to the analysis and permits reasonable comparison with other programs.

SUMMARY AND CONCLUSIONS

These results demonstrate that it is possible to achieve low early infant infection rates (<5%) through delivery of comprehensive PMTCT services and combination ARVs in resource-limited setting.

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