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Original Article

Outcomes of prevention of HIV mother-to-child transmission in Cipto Mangunkusumo Hospital

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Abstract

Background Human immunodeficiency virus (HIV) infection is increasing worldwide. One route of HIV transmission is from mother to child, during pregnancy, delivery or breastfeeding. Prevention of mother-to-child transmission may be an effective strategy to reduce the cases of new HIV infections.

Objectives To investigate the incidence of HIV infection in infants born to mothers with HIV and who received prophylactic therapy at birth, as well as to note the outcomes of HIV-infected children in this program.

Methods This retrospective study was carried out over a 9-year period, from January 2003 to December 2011. The participants were HIV-exposed infants who attended the HIV clinic, at the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta. Infants were treated according to the prevention of mother-to-child transmission (PMTCT) protocol at CMH. Parents' and infants' data was recorded. The end point of this study was recording of HIV-infection status in the infants.

Results There were 238 infants included in this study. HIV infection was confirmed in 6 (2.5%) infants, while 170 (71.4%) subjects were uninfected, and 62 (26.1%) subjects were lost to follow-up. No subjects who underwent complete PMTCT management were infected. Most subjects were male, full-term, and delivered by caesarean section in our hospital. The most frequently observed parental risk factor was intravenous drug use. Maternal antiretroviral therapy (ART) was given during pregnancy in most cases. Morbidities in all subjects were low.

Conclusion The PMTCT program at CMH was effective for reducing the number of HIV-infected infants from mothers with HIV. **[Paediatr Indones. 2012;52:294-9]**.

Keywords: *HIV mother-to-child transmission, HIV, prevention*

The human immunodeficiency virus (HIV) epidemic continues to affect women and children worldwide. The 2001 United Nations General Assembly Special Session (UNGASS) targeted a 50% reduction in HIV-infected infants by 2010.[1] Most HIV-infected children get the infection through mother-to-child transmission (MTCT), which can occur during pregnancy, delivery, or breastfeeding. Without intervention, the risk of transmission was reported to be 15–30% in non-breastfeeding populations. Breastfeeding by an infected mother increased the risk up to 25–45%.[2]

The rate of mother-to-child HIV transmission globally was estimated to decline from 35% in 2001, to 29% in 2009, and 26% in 2010.[3] These reduction was attributable to the Prevention of Mother-to-Child Transmission of HIV program, a comprehensive approach promoted by the World Health Organization (WHO). The program consisted of 4 components: (1) primary prevention of HIV infection, (2) prevention of unintended pregnancies in women with HIV, (3) prevention of HIV transmission from mothers with HIV to their infants, and (4) care, treatment and

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support for mothers with HIV, their children, and families.[1]

Strategies to prevent the transmission included maternal and infant ART therapy, elective caesarean section, and avoidance of breastfeeding. These combined interventions reduced the rate of transmission to less than 2%.[1,4] Indonesian HIV cases were predominantly people of reproductive age, 28% of whom were women.[5] As more women were infected, the probability of passing the infection to their children increased. Cipto Mangunkusumo Hospital is one of the largest centers for pediatric HIV in Indonesia, and has focused efforts on the PMTCT program. In a preliminary report on the PMTCT program, the rate of HIV transmission in the hospital was 3 out of 17 infants in 2003-2004.[6] The rate of transmission was not evaluated again after this time. The objective of our study was to investigate the incidence of HIV-infected infants born to mothers with HIV and who had received prophylactic therapy at birth, as well as the morbidity of HIV- infected children in the PMTCT program.

Methods

This 9-year retrospective study included HIV-exposed infants who attended the HIV clinic at the Department of Child Health, Cipto Mangunkusumo Hopital, Jakarta from January 2003 to December 2011. Infants were born either in our maternity department or other hospitals and aged less than 2 weeks. Infants were treated according to the PMTCT protocol in CMH. We gave ART to the infants, consisting of zidovudine for 6 weeks and a single dose nevirapine. Infants received formula feeding after parental consent. Maternal data collected included risk factors, mode and time of delivery, time of ART (before pregnancy, during pregnancy, during delivery, or no ART). Paternal risk factors were also recorded. Infant data included gender, infection status and morbidities. After the age of 4 weeks, infection status was determined by polymerase chain reaction (PCR) on ribonucleic acid (RNA) testing. After 18 months of age, infection status was tested by serology.

The endpoint of this study was the HIV-infection status in infants. Infants were determined to be infected if they were HIV-positive by PCR RNA testing after 4 weeks of age, or by serology after 18 months of age. Uninfected infants underwent a minimum of one PCR RNA HIV test after 4 weeks of age. Subjects who attended our clinic for less than 6 months were considered to be lost to follow up. Data was extracted from the medical records and analyzed by SPSS version 15.

Results

There were 238 infants included in this study and 62 (26.1%) subjects were lost to follow up. HIV infection was confirmed in 6 (2.5%) infants. None of the infants of mothers who underwent complete PMTCT management (maternal ART before or during pregnancy, caesarean section, and formula feeding) were infected. The number of infants in our PMTCT program increased yearly until 2007, after which it decreased (**Figure 1**).

Most subjects were male, full-term, and delivered by caesarean section in our hospital. The most frequently observed parental risk factor was intravenous drug use (**Table 1**).

Maternal ART was given during pregnancy in most cases. Morbidities of our subjects were very low (**Table 2**). The most common morbidity was upper respiratory tract infection, followed by acute diarrhea and dermatitis. All subjects survived.

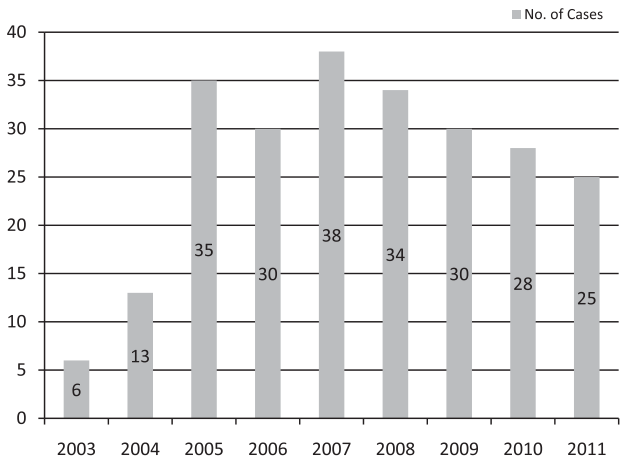

Figure 1. Number of infants in the PMTCT program in CMH from 2003-2011 (n= 238)

Table 1. Subjects' characteristics

Characteristics	n=238
Gender, n (%)	
Males	125 (52.5)
Female	113 (47.5)
Place of birth, n (%)	
Cipto Mangunkusumo Hospital	197 (82.8)
Other hospitals	41 (17.2)
Maternal/paternal risk factors, n (%)	
IVDU*	160 (67.2)
MSP+	32 (13.4)
IVDU and MSP	7 (2.9)
Sexual abuse	1 (0.4)
Tattooing	1 (0.4)
Unknown	37 (15.5)
Mode of delivery, n (%)	
Caesarean section	224 (94.1)
Vaginal	14 (5.9)
Gestation, n (%)	
Full term	229 (96.2)
Premature	9 (3.8)
Maternal ART, n (%)	
Before pregnancy	51 (21.4)
During pregnancy	105 (44.1)
During delivery	8 (3.4)
No ARV	26 (10.9)
Unknown	48 (20.2)

* IVDU: intravenous drug use;
+MSP: multiple sex partners

Table 2. Known morbidities of infants in the PMTCT program*

Morbidities	n (%)
Upper respiratory tract infection	30 (12.6)
Acute diarrhea	16 (6.7)
Dermatitis	15 (6.3)
Anemia	7 (2.9)
Oral candidiasis	7 (2.9)
Impetigo	2 (0.8)
Pneumonia	1 (0.4)
Perinatal tuberculosis	1 (0.4)
Chronic diarrhea	1 (0.4)

* Subjects may have more than one morbidity.

All six HIV-infected infants were delivered by caesarean section (CS) and were full-term. Maternal ART during pregnancy was not given in four infants, while in the other two cases, mothers received intrapartum ART. Three of infected cases remain on active follow up and two of them were on second line ART (**Table 3**).

Discussion

The PMTCT program has been an effective approach to decrease the number of newly HIV-infected infants. Management of infants born to HIV-infected mothers included nutritional management, prophylactic ART, immunizations, opportunistic infection prophylaxis, as well as growth and developmental monitoring (**Figure 2**).[7]

There were 238 mother-infant pairs in our study. The yearly number of cases increased until 2007, and decreased in subsequent years. The number of patients was decreased after 2007, because more HIV-infected mothers were treated elsewhere as a result of extended care and treatment for HIV-infected mothers in national program.

Most infant subjects were male, full-term, and delivered by caesarean section in CMH. Caesarean section may minimize HIV transmission during delivery. Read *et al*[8] showed that elective caesarean section effectively decreased HIV transmission to infants, especially among among HIV-1-infected women who did not take ART or took only zidovudine. However, postpartum morbidity was higher among HIV-1-infected women who underwent caesarean than those who delivered vaginally. We did not evaluate postpartum morbidity in our study.

The most frequently observed parental risk factor was intravenous drug use. In contrast, the Indonesian

Table 3. Description of HIV-positive cases

Case	Maternal ART	Mode of delivery	Time of delivery	Infant viral load at age 4-6 weeks, copies/mL	Recent ART therapy	Recent status
1	No	CS	Full-term	246,509	AZT/3TC	LTFU*
2	Intrapartum	CS	Full-term	8,850	AZT/3TC/NVP	LTFU
3	No	CS	Full-term	32,526	ddI/3TC/LPV/r	Healthy
4	Intrapartum	CS	Full-term	1,977,860	AZT/3TC/NVP	LTFU
5	No	CS	Full-term	1,587,781	ddI/3TC/LPV/r	Healthy
6	No	CS	Full-term	203,741	d4T/3TC/NVP	Healthy

Note: Cases 3 and 5 were recognized as treatment failure at 23 and 66 months, respectively.
*LTFU: lost to follow up; AZT: zidovudine; 3TC: lamivudine; NVP: nevirapine; ddI: didanosine; LPV: lopinavir; r: ritonavir; d4T: stavudine

	Born	10 days	4 weeks	6 weeks	2 mos	3 mos	4 mos	6 mos	9 mos	18 mos
Body weight/ body height										
Nutrition	FF	FF	FF	FF	FF	FF	FF	FF-SF	FF-SF	FF-SF
ARV prophylaxis										
Co-trimoxazole										
Immunizations	According to Ministry of Health/Indonesian Pediatric Society schedule Special precaution: BCG									
Hb/Ht										
PCR RNA/DNA			1				2			AB

FF: formula feeding; SF: solid food; Hb: hemoglobin; Ht: hematocrit;
PCR RNA/DNA: polymerase chain reaction RNA/DNA; AB: HIV antibody; ARV: antiretroviral

Figure 2. PMTCT schedule in Cipto Mangunkusumo Hospital

Ministry of Health reported that intravenous drug use was second after multiple sex partners.[5] Risk factors in Indonesia differ from region to region.

We found the rate of confirmed HIV-transmission to be 2.5%, comparable to other studies in developing countries.[1] All mothers of the infected subjects did not receive ART before or during pregnancy. Lallemant *et al*[9] found that the rate of in utero transmission was significantly higher with shorter maternal ART (5.1%), than with longer maternal treatment (1.6%). Lussiana *et al*[10] also found that maternal HIV transmission in mothers with ART was lower than in mother s without ART during pregnancy (1.5% vs 37.1%, respectively).

The importance of maternal ART to prevent mother-to-child HIV transmission was reported by Sturt *et al*. They demonstrated that in ART-eligible pregnant women with HIV infection, ART was safe and effective for providing maternal virologic suppression, decreasing infant mortality, and reducing mother-to-child transmission. ART given for a minimum at 28 weeks gestation was more beneficial than that given short term.[11] All HIV-infected cases in our study were not exposed to maternal ART during pregnancy.

According to the WHO 2010 recommendation, antiretroviral prophylaxis for HIV-exposed infants depends on choice of nutrition (breastfeeding or non-breastfeeding) and history of maternal ART. All non-breastfeeding infants should receive zidovudine or nevirapine from birth until 6 weeks of age. For infants born to HIV-infected mothers receiving ART for the mothers' own health and were breastfed, nevirapine should be given from birth until 6 weeks of age. However, if mothers do not need treatment for their own health and their babies are breastfed, babies should receive nevirapine from birth until one week after all exposure to breast milk has ended.[12]

We gave ART to infants, consisting of zidovudine for 6 weeks at a dose of 2 mg/kg body weight and a single dose of nevirapine at 2 mg/kg body weight. This combination protocol was from the PACTG 76 protocol[13] and a study from Thailand.[14] This recommendation was changed in 2012, but it was similar to the WHO 2010 recommendation where we gave only zidovudine for 6 weeks.[12]

Nutritional management in infants of HIV-infected mothers is complex. Breastfeeding increased HIV transmission up to 25-45%.[2] Replacement feeding with infant formula prevents all transmission of HIV through breastfeeding, but in some resource-limited settings, formula feeding may also increase the risk of death from causes other than HIV, such as malnutrition, pneumonia, and diarrhea.[15] Therefore, the risk of infants acquiring HIV through breastfeeding must be evaluated in light of the risk of death from causes other than HIV.

All HIV-exposed newborns in this study were formula fed, with consent from their parents. We

observed no mortality in our subjects. The morbidity rate was low, and comparable to non-HIV exposed infants. The Mashi study showed that the 7-month HIV infection rates were 5.6% in the formula-fed group and 9.0% in the breastfeeding plus zidovudine group (P=0.04). Cumulative infant mortality at 7 months was significantly higher for the formula-fed group than for the breastfed plus zidovudine group (9.3% vs 4.9%, respectively; P=0.003), but this difference diminished after month 7. The cumulative HIV infection rate at 18 months were 6% in the formula-fed group and 9.5% in the breastfed plus zidovudine group (P=0.02). Whereas, the cumulative mortality rate at 18 months were 10.7% in the formula-fed group and 8.5% in the breastfed plus zidovudine group (P=0.21). [16]

Three out of six HIV-infected infants were in active follow up. Two used second line ART. Treatment failure may have resulted from incomplete viral suppression due to non-adherent patients or nevirapine-resistance due to exposure to a single dose of nevirapine after birth. Arrive *et al*.[17] found in their meta-analysis that pooled estimates of nevirapine resistance in children who were exposed to single-dose nevirapine was 52.6% (CI 37.7–67.0), while that in children who were exposed to single-dose nevirapine with other antiretrovirals was only 16.5% (CI 8.9–28.3).

In conclusion, the rate of HIV transmission from mother-to-child in this study was low, and none of the subjects who underwent complete PMTCT management were infected. These results were comparable to other studies in developing nations. Implementation of comprehensive PMTCT strategies should be done in Indonesia to decrease the incidence of mother-to-child HIV transmission.

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