

HIV-free Survival at the Age of 18 Months in Children Born to Women With HIV Infection: A Retrospective Cohort Study

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Objective: To assess HIV-free survival and nutritional status of HIV-exposed infants. **Methods:** This retrospective cohort study was conducted on infants born to woman with HIV infection born at our Institute between January 2011 to March 2016, and followed using current National guidelines. HIV transmission rate, HIV-free survival, and nutritional status were assessed 18 months age. **Results:** Of the 155 infants, 10 (6.5%) died before 18 months of age. Two of 145 surviving infants were confirmed HIV-positive, the remaining were HIV-negative at 18 months (HIV-free survival 92.3%). Of the 10 infants who died, one was confirmed HIV-positive and three negative; the rest died before their HIV status could be ascertained. HIV infection rate among the 149 infants for whom the test reports were available was 2%. At 18 months age, 14% HIV-uninfected infants were wasted, 28% stunted, and 3% had microcephaly. **Conclusions:** Infants born to mothers with HIV managed as per the current National guidelines have a good outcome at 18 months of age.

Key words: HIV exposure, infants, Malnutrition, Outcome.

Exposure to the same adverse environment places HIV-exposed infants at a higher risk of morbidity and mortality regardless of their own HIV status, as compared to infants born to women without HIV infection [1,2]. The survival and health of these infants are influenced by the feeding strategy adopted, higher exposure to infections, and HIV-status of the infant himself [3,4]. A high mortality in these children has previously been reported from this setting [5].

The current prevention of parent to child transmission (PPTCT) guidelines by National AIDS Control Organization (NACO), recommend lifelong anti-retroviral therapy (ART) to all pregnant and breast-feeding women with HIV regardless of clinical or immunological stage, anti-retroviral (ARV) prophylaxis to the baby, and safe infant feeding practices. A well-defined protocol has also been developed for care of the HIV-exposed infants [6]. The objective of this work is to report outcome of HIV-exposed infants born at a tertiary-case pediatric hospital, and provided standardized care as per the current NACO protocol.

METHODS

This retrospective cohort study was conducted in the Pediatric Centre of Excellence in HIV care located at a public teaching hospital in northern India. Infants born to women with HIV infection at the linked hospital and

registered in the PPTCT program at our Centre from January 2011 to March 2016 were included. We excluded infants born at other hospitals and subsequently referred to our Centre, those diagnosed with HIV after admission to our pediatric wards, or those who never attended the Centre after birth at the linked hospital.

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In accordance with the National guidelines, the HIV-exposed infants are registered at birth in our Centre and given a protocol-based care till 18 months of age [6]. This includes provision for early HIV diagnosis, safe feeding counselling, and access to routine infant care practices. Prior to January 2014, all women with HIV and their newborns were given a single dose of nevirapine (SDNVP) during labor and immediately after birth, respectively, in accordance with the national guidelines at that time [7]. After January 2014, all pregnant women with HIV are initiated on ART during pregnancy soon after detection of their HIV status. Infants born to these women are started on daily nevirapine prophylaxis at birth and continued for a minimum of 6 weeks [6]. This study included subjects registered both before and after these changes in the National recommendations. Determination of HIV status was done through HIV-1 DNA-PCR by dried blood spot (DBS) at ages 6 weeks, 6 months, and six weeks after stopping breastfeeding.

Infants testing positive on DBS testing were re-tested for DNA-PCR on whole blood sample. In infants older than 18 months, serological tests (3 rapid antibody tests) were done for HIV diagnosis.

For the current study, information on maternal and infant characteristics was obtained from the records of all eligible infants maintained at our Centre. The nutritional status of children was determined by calculating Z-scores for weight for age (WFA), weight for length (WFL), length for age (LFA) and head circumference for age (HFA) using WHO growth reference standards [8].

The infants were considered to be HIV-infected if they tested positive on DNA-PCR any time before 18 months, or were found reactive on HIV serology at 18 months or beyond. They were considered HIV-uninfected if they had a negative DNA-PCR test and were not breastfeeding or had stopped it 6 weeks prior to the test, or had a non-reactive HIV serological test at or after 18 months performed at least 6 weeks after cessation of breastfeeding. The study was approved by the Institutional Ethics Committee for Human Research.

Statistical analysis: The data were analyzed using the SPSS statistical software package, Version 23. Chi square test, unpaired t test and Mann-Whitney U test were used to compare maternal and infant variables among HIV- uninfected infants at 18 months and those who died.

RESULTS

During the study period, 165 HIV-exposed infants were born at the linked hospital. Among these, 155 mother-infant pairs who were followed up at our centre till 18 months were eligible for the study. The clinical characteristics of these mother infant dyads are shown in **Table I**.

Of the 155 infants, 10 (6.5%) died before 18 months of age. Among the 145 surviving infants, two were confirmed HIV-positive. The rest 143 (92.3%) were surviving and HIV-free at 18 months. Of the 10 infants who died before 18 months, one had positive and three had negative HIV DNA-PCR at the age of 6 weeks (all 3 on exclusive replacement feeds), while the rest died before their HIV status could be ascertained (**Fig. 1**).

HIV infection was reliably excluded in 146/155 infants (143 of those alive and 3 of those who died) while it was diagnosed in 3 infants (2 of those alive and 1 among those who died). Thus, HIV infection rate in the infants for whom the HIV test reports were available was 2% (3/149). On analyzing the data before ($n=93$) and after ($n=62$) the change in PPTCT guidelines, no significant difference was found in terms of HIV-free

survival (92.5% vs 91.9%; $P=0.9$); or HIV transmission rate (2.2 vs 1.7 %; $P=0.82$).

The outcome in terms of survival and status of HIV infection stratified as per various maternal and infant factors is presented in **Table II**. Details of the three infants who were diagnosed with HIV infection are presented **Web Table I**.

At the age of 18 months, Z scores for WFL ($n=108$), LFA ($n=108$) and OFC ($n=106$) were -0.6 (1.2) , -1.2 (1.2), and -0.9 (1.2), respectively. At that time, 15 (14%) of uninfected infants were wasted, 30 (28%) infants were stunted, and 3 (3%) had microcephaly.

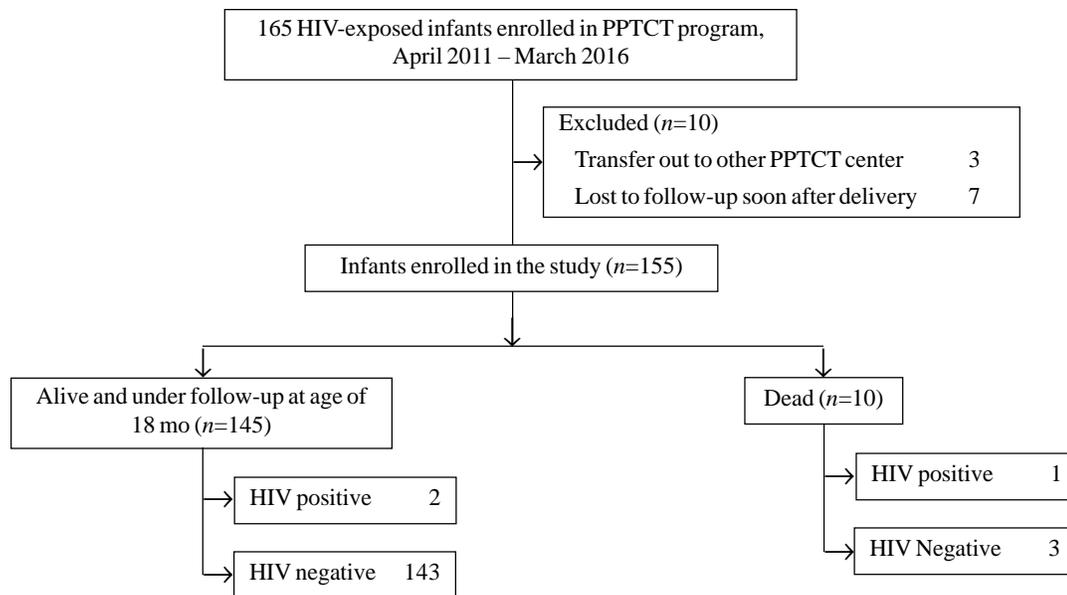
DISCUSSION

The present study has documented HIV infection rate and HIV-free survival among infants of women with HIV infection managed as per national PPTCT strategy. Parent to child transmission rate in the present study was 2%, with an overall ARV cover in HIV positive mothers of 94% (ART 79%, SDNVP 15%). We have previously reported a rate of 14.8% when the ARV cover in HIV-infected mothers was only 61.5% [5]. The current transmission rate is also much less when compared to studies from Africa [9,10], as well as few studies from India where the transmission rate has varied between 8-19% [11,12].

TABLE I CLINICAL CHARACTERISTICS OF INFANTS BORN TO MOTHERS WITH HIV INFECTION ($N=155$)

Characteristics	No. (%)
Male	82 (53)
<i>Mother's HIV diagnosis</i>	
Before pregnancy	72 (46)
During pregnancy	77 (50)
After delivery	6 (4)
<i>Mother's therapy status at delivery</i>	
*On triple ART	123 (79)
#Single dose nevirapine	23 (15)
No ART/ARV	9 (6)
<i>Infant feeding status</i>	
Exclusive breast feeding	82 (53)
Exclusive replacement feeding	71 (46)
Mixed feeding	2 (1)
<i>Anthropometry at birth, mean (SD)</i>	
WFL Z-score	-1.2 (1.4)
LFA Z-score	-0.7 (1.1)
OFC Z-score	-1.0 (1.1)

*Known HIV: infected before pregnancy: *68/72 and #4/72; HIV: positive detected during pregnancy: *55/77 and #19/77; OFC: Occipito-frontal circumference; LFA: Length for age; WFL: Weight for length.*



*Causes of death: In infant with HIV infection: severe malnutrition with sepsis; for the 3 infants who were HIV negative: prematurity with aspiration, prematurity with pneumonia and unknown in 1 case each; for the remaining 6 infants with unknown HIV status: sepsis, severe diarrhea, sudden infant death syndrome and road accident in 1 infant each and unknown in 2 infants.

FIG. 1 Outcome of HIV-exposed infants enrolled in the study.

TABLE II OUTCOME OF INFANTS STRATIFIED ACCORDING TO MATERNAL AND INFANT CHARACTERISTICS (N=155)

Characteristics	Total	Alive at 18 mo (n=145)		Death (n=10)
		Infected (n=2)	Not infected (n=143)	
<i>Maternal ART/ARV at the time of delivery, n (%)</i>				
On ART	123 (79)	2 (100)	114 (80)	7 (70)
On ARV prophylaxis	23 (15)	0	23 (16)	0
Not on ART/ARV or started after delivery	9 (6)	0	6 (4)	3 (30)
*ART duration, mo	6 (2.3-24)	17.5 (1-17.5)	6 (3-23.3)	2 (0.8-35)
#Vaginal delivery	70 (45)	2 (100)	60 (42)	8 (80)
Maternal CD4 count, cells/mm ³ , mean (SD)	359 (191.9)	259 (55.2)	365.7 (196.1)	300 (142.9)
<i>‡Infant prophylaxis, n (%)</i>				
Single dose Nevirapine	40 (26)		37 (26)	3 (30)
Nevirapine for 6 wk	86 (55)	1 (50)	81 (57)	4 (40)
Nevirapine ≥12 wk	28 (18)	1 (50)	24 (16.8)	3 (30)
Birthweight (kg), mean (SD)	2.6 (0.5)	2.6 (0.6)	2.6 (0.4)	2.1 (0.7)
<i>§Feeding during first 6 mo, n (%)</i>				
Exclusive breastfeeding	82 (53)	2 (100)	76 (53)	4 (40)
Replacement feeding	71 (46)		65 (45)	6 (60)
**Maternal CD4 < 350 cells/mm ³ , n (%)^	70 (56)	2 (100)	61 (53)	7 (78)

*Value in median (IQR); HIV-uninfected surviving infants and dead infants; P values of #0.02 and **0.002; ^Available for 126 infants including the 2 infected infants, 115 alive uninfected infants and 9 dead infants; ‡One infant did not receive prophylaxis; §two infant were on mixed feeding.

WHAT THIS STUDY ADDS?

- Implementation of the current Prevention of parent-to-child transmission (PPTCT) strategy and a structured follow up of HIV-exposed infants results in an HIV-free survival matching that observed in more developed countries.

TABLE III DETAILS OF INFANTS DETECTED HIV-INFECTED

Case number	Mother's details		Infant prophylaxis	Feeding (total duration)	Infant HIV testing			Outcome
	Prophylaxis (duration before delivery)	Pre-delivery CD4 counts (cells/mm ³)			6 wk	6 mo	18 mo	
1	ART (2 y 10 mo)	220	Nevirapine for 6 wk	Breastfeeding (13 mo)	DBS* negative	DBS negative	Serology positive	Alive/ on ART
2	ART (1 mo)	298	Nevirapine for 12 wk	Breastfeeding (16 mo)	Not done	Serology negative	Serology positive	Alive/ on ART
3	ART (4 mo)	334	Single dose nevirapine	Replacement feeding	DBS positive	-	-	Died at 3 mo of age (severe sepsis)

*DBS: Dried blood sample.

These studies were conducted during the time when most mothers received SDNVP, ART being limited only to those eligible as per their clinical/immunological criteria. In a recent study, where 37% of HIV-infected pregnant women received ART, and 63% SDNVP, Seenivasan, *et al.* [13] have reported a HIV transmission rate of 4%. Another study from this region, where 92% of enrolled women were getting either ARV prophylaxis or ART, a HIV transmission rate of 3.4% was reported [14]. The results of the current and these other recent studies from India show that with current robust PPTCT strategy, the HIV transmission rate in India is approaching the rate observed in developed countries (1-2%) [15,16].

We observed a 92.3% HIV-free survival at 18 months of age, similar to a recent study from Rwanda [17] that reported a 24-month HIV-free survival of 93.2% in breastfeeding infants of HIV-positive mothers on lifelong ART. A systematic review including 18 studies published between 2005 to 2015 provided a pooled estimate of 18-month HIV-free survival of 89.0% with 6 months ART and 96.1% with lifelong ART [18]. The authors found that the HIV-free survival, though higher in the breastfeeding group, did not significantly differ by feeding patterns. Similar findings were also observed in the present study. At 18 months, the prevalence of wasting and stunting among infants was no different from that reported among Indian children of this age group as per NFHS-4 [19].

Several reasons contribute towards better outcome of HIV-exposed infants in terms of survival, HIV transmission and nutritional status in the current as

compared to our previous study [5]. Unlike the previous study, the present work excluded infants diagnosed as HIV-exposed/infected after birth. A much higher proportion of mothers were on ART (79%) as compared to the previous study (17.4%). Provision of a protocol-based care with focus on repeated counselling to optimize health of mother-infant dyad also contributed to the improved outcome.

Due to a small number of infants who acquired HIV infection or died, our results give limited information regarding predictors of HIV infection transmission/mortality in HIV-exposed infants. As routine viral load was not introduced in the national protocol during this study period, maternal viral load, that directly impacts upon the HIV transmission rate, could not be assessed.

We conclude that implementation of the current PPTCT strategy, which includes lifelong ART to all HIV-infected pregnant and breastfeeding women with ARV prophylaxis to their infants, and a structured follow up of HIV-exposed infants, has remarkably improved the outcome of these infants.

Contributors: NB: managed the cases, recorded the information and drafted the paper; AS: conceptualized the paper, drafted and edited the manuscript and was the consultant in patient management. She will be the corresponding author for this work; SS: contributed towards design of the work, data analysis and manuscript preparation; GS: provided clinical care to study subjects, and contributed towards record keeping and manuscript preparation; PK, JC: consultants in patient management and helped in drafting /editing the paper. All

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REFERENCES

- Landes M, Lettow MV, Chan AK, Mayuni I, Schouten EJ, Bedell RA. Mortality and health outcomes of HIV exposed and unexposed children in a PMTCT cohort in Malawi. *PLoS One*. 2012;7:e47337.
- Slogrove A, Reikie B, Naidoo S, Beer CD, Ho K, Cotton M, *et al.* HIV exposed uninfected infants are at increased risk for severe infections in the first year of life. *J Trop Pediatr*. 2012;58:505-8.
- Ram M, Gupte N, Nayak U, Kinikar AA, Khandave M, Shankar AV, *et al.* Growth patterns among HIV-exposed infants receiving nevirapine prophylaxis in Pune, India. *BMC Infect Dis*. 2012;12:282.
- Sobze MS, Wadoum RG, Temgoua E, Donfack JH, Ercoli L, Buonomo E, *et al.* Evaluation of the nutritional status of infants from mothers tested positive to HIV/AIDS in the health district of Dschang, Cameroon. *Pan Afr Med J*. 2014;18:91.
- Seth A, Chandra J, Gupta R, Kumar P, Aggarwal V, Dutta A. Outcome of HIV exposed infants: Experience of a regional pediatric center for HIV in North India. *Indian J Pediatr*. 2012;79:188-93.
- Updated guidelines for Prevention of Parent to Child Transmission (PPTCT) of HIV using multi drug Anti-retroviral regimen in India. December, 2013. National AID Control Organization. Available from http://naco.gov.in/sites/default/files/National_Guidelines_for_PPTCT_0.pdf. Accessed April 04, 2018.
- Guidelines for HIV care and treatment in infants and children 2006. Available from <http://apps.who.int/mediacinedocs/documents/s18022en/s18022en.pdf>. Accessed April 04, 2018.
- WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for age: methods and development. Geneva: World Health Organization, 2006. Available from http://www.who.int/childgrowth/standards/technical_report.pdf. Accessed April 04, 2018.
- Birlie B, Diriba TA, Sisay K, Gurmessa A, Seyoum D, Tadesse M. Mother to child HIV transmission and its predictors among HIV-exposed infants: A retrospective follow-up study in southwest Ethiopia. *J AIDS Clin Res*. 2016;7:605.
- Ng'ambi WF, Ade S, Harries AD, Midiani D, Owiti P, Takarinda KC, *et al.* Follow-up and programmatic outcomes of HIV-exposed infants registered in a large HIV centre in Lilongwe, Malawi: 2012–2014. *Trop Med Int Health*. 2016;21:995-1002.
- Mukherjee S, Ghosh S, Goswami DN, Samanta A. Performance evaluation of PPTCT (Prevention of parent to child transmission of HIV) programme: An experience from West Bengal. *Indian J Med Res*. 2012;136:1011-9.
- Malpani P, Biswas M, Kale V. Outcome of children born to human immunodeficiency virus positive mothers- A retrospective study. *Indian Journal of Child Health*. 2016; 3:244-7.
- Seenivasan S, Vaitheeswaran N, Seetha V, Anbalagan S, Karunaianantham R, Swaminathan S. Outcome of prevention of Parent-To-Child Transmission of HIV in an urban population in Southern India. *Indian Pediatr*. 2015; 52:759-62.
- Dwivedi S, Jahan U, Dwivedi GN, Gupta N, Verma K, Sharma B, *et al.* Perinatal outcome in HIV infected pregnant women at tertiary care hospital in North India: Eleven years retrospective study. *International Journal of Recent Scientific Research*. 2017;8:16801-5.
- Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS*. 2008;22:973-81.
- Centers for disease control and prevention: Achievements in public health. Reduction in perinatal transmission of HIV infection-United States, 1985–2005. *MMWR Morb Mortal Wkly Rep*. 2006;55:592-7.
- Gill MM, Hoffman HJ, Ndatimana D, Mugwaneza P, Guay L, Ndayisaba GF, *et al.* 24-month HIV-free survival among infants born to HIV-positive women enrolled in Option B+program in Kigali, Rwanda: The Kabeho study. *Medicine (Baltimore)*. 2017;96:e9445.
- Chikhungu LC, Bispo S, Rollins N, Siegfried N, Newell ML. HIV-free survival at 12 - 24 months in breastfed infants of HIV-infected women on ART. *Trop Med Int Health*. 2016;21:820-8.
- International Institute for Population Sciences (IIPS) and ICF. 2017. National Family Health Survey (NFHS-4), 2015-16. India. Mumbai: IIPS.