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Dr. Ravindra Thakur
PG, Department of Obstetrics & Gynaecology, NSCB Medical College, Jabalpur, Madhya Pradesh, India

Dr. Archna G Singh
Associate Professor Department of Obstetrics & Gynaecology, NSCB Medical College, Jabalpur, Madhya Pradesh, India

Dr. Vineeta Ghanghoriya
Assistant Professor Department of Obstetrics & Gynaecology, NSCB Medical College, Jabalpur, Madhya Pradesh, India

Dr. Pawan Ghanghoriya
Professor & HOD Department of Obstetrics & Gynaecology, NSCB Medical College, Jabalpur, Madhya Pradesh, India

Correspondence
Dr. Archna G Singh
Associate Professor Department of Obstetrics & Gynaecology, NSCB Medical College, Jabalpur, Madhya Pradesh, India

Early infant diagnosis (EID): A vital component of prevention of parent to child transmission program

Dr. Ravindra Thakur, Dr. Archna G Singh, Dr. Vineeta Ghanghoriya and Dr. Pawan Ghanghoriya

Abstract
Background: Early diagnosis of HIV infection in exposed infants and children is essential component to child survival. EID, a virological DNA PCR test on dried blood spot, aims at early diagnosis and ART initiation, breast feeding choices and linkage to care. It confers substantial benefit to the infected and uninfected infants and provides a unique opportunity to evaluate the performance of PPTCT program.
Materials and method: Present study conducted in the department of Obstetrics and Gynecology, NSCB Medical College, Jabalpur from March 2016 to August 2017. HIV exposed infants and children between 6 weeks to 18 months of age were included. HIV testing (DNA PCR and antibody tests) done at 6weeks, 6, 12 and 18 months as per pediatric ART guidelines of NACO, 2015.
Results: Total 145 infants/children were tested during study period. 8 found to be HIV positive which gives an incidence of 5.51% in out institute.112 (80.7%) had first visit between 6 weeks to 6 months.130(89.6)% mother-baby pair received ART/ARV prophylaxis. Transmission rate lowest (0.76%) in Mother-baby pair who received ART. 69(47.9% infants were on replacement feeding. The transmission rate was (8.1%). One death observed and 12 (8.27%) lost to follow up. EID results at first contact were accurate and well correlated with the results at 6, 12 and 18 month.
Conclusion: EID is a vital component of PPTCT program. It confirms the diagnosis as early as 6 weeks and confers an accurate and consistent results throughout testing protocol, thus establishing the integrity of EID. It assists in decision making on infant feeding practices.

Keywords: Dried blood spot, early infant diagnosis, human immunodeficiency virus, prevention of parent to child transmission

Introduction
India has successfully achieved the 6th millennium developmental goal of halting and reversing the HIV epidemic. Between 2000 and 2015 new HIV infections dropped from 2.51 lakhs to 86 thousand, a reduction of 66% against global average of 35.5% [1, 2]. Despite the strengthened PPTCT interventions mother to child transmission of HIV accounts for the vast majority of paediatric infections and is still a major cause of infant and childhood morbidity and mortality [3]. National programmes that are able to report by age reveal that very few of these children are under 2 years of age. Mortality is high among HIV- infected infants in the first year of life particularly when there is no access to life saving drugs, antiretroviral therapy (ART) and Co-trimoxazole prophylaxis (CPT) [4]. Affordable ART and treatment are becoming increasingly available but is of less benefit in infants unless they can be diagnosed early. Most widely available serological assays used for adult pose difficulty in interpretation in infants aged under 9-12 months owing to passage of maternal antibodies [5] Early diagnosis of HIV allows health care providers to offer optimal care and treatment of HIV exposed infants and children, assists in decision making on infant feeding choices and avoids needless stress in mothers and families. Virological testing is therefore a required method of diagnosis of HIV in infancy. EID, a validated recommendation of NACO is a virological test (DNA PCR) which uses dried blood spot (DBS) for early infant diagnosis of HIV [6].
We undertook this study to find out the serostatus of HIV exposed infants and children at first contact and to correlate the EID results with HIV result at 18 months.

Methodology
This prospective observational longitudinal study was conducted in the department of Obstetrics and Gynaecology NSCB, Medical College & Hospital, Jabalpur (MP) from March 2016 to August 2017 after seeking approval from the institutional ethical committee

Inclusion Criteria

1) HIV exposed infants /children delivered in the department of Obstetrics and Gynaecology NSCB, Medical College or elsewhere and came for follow-up or as referred case, for EID, between 6 weeks to 18 months of age.
2) Children with sign & symptoms of HIV or on ART based on presumptive diagnosis.

Parents written informed consent was obtained. The NACO guideline 2015 for EID of HIV was followed through out. As a routine protocol all the infants borne to the HIV positive mothers, in the department, irrespective of ART, were given single dose Nevirapine (sdNvp) within 72 hours of birth. These mothers were advised to visit PPTCT clinic with the child 6 weeks following delivery.The scheduled visits for HIV exposed infants/children for testing were at age 6 weeks, 6, 12, 18 months or six weeks after cessation of breastfeeding.

At the first visit (6weeks) detail history including demographic profile, date of birth, type of delivery, breast feeding practices and ART were noted.Written informed consent of parents/guardians, following appropriate pretest counseling was obtained for diagnostic tests of HIV on their child's specimen. Study population was divided into two groups according to the age of first visit.

Group A included infants aged between 6 weeks to 6 months. Group B included children beyond 6 months and upto 18 months. In Group A blood specimen was collected by a heel prick with proper aseptic precautions. Dried blood spots were prepared on DBS card and sent for HIV-1 PCR testing at Molecular Biology Laboratory Mumbai. If DBS negative for HIV, infant was followed up to 18 months. If positive, another DBS collected and sent for confirmatory HIV-1 PCR test. If second DBS positive, infant was referred to ART centre in our institute for further management. If second DBS negative, another sample was sent for second confirmatory HIV-1 PCR test, the result of which was counted for further management.

In Group B serum sample was tested for HIV antibodies using all 3 serological tests. Also a DBS was prepared. If the result was negative the child was followed up at PPTCT clinic until 18 months. In case positive, DNA PCR was done on DBS specimen. If Antibody Reactive on all 3/2/1 of the three tests DBS sample was sent for HIV-1 PCR test and the procedure was followed as earlier. All the exposed children who were negative at the first contact were tested on subsequent scheduled visits. Irrespective of HIV status all were continued with CPT prophylaxsis till 18 months. All relevant information was collected from EID register at PPTCT clinic. At the end of study period all the data were compiled and analyzed.

Definitive diagnosis was ensured at 18 month or 6 weeks following cessation of breastfeeding using antibody tests. Throughout the study period confidentiality was maintained. Kits used during study period were Combat, Mariscan and Aidscan. Statistical analysis done using Chi square test and Sample size estimation for proportion formula n=z2pq/d2

Where z=1.96 at 5%, alpha, 80% power and 95%CI

p=10.26%, q=I-p, d=5% absolute precision

Results

Total 145 children were registered, out of which 8 were HIV positive (5.51%). 117(80.7%) babies had first visit between 6weeks-6 months of age. (Table 1). 130(89.6%) mother- baby pair received ART/ARV prophylaxis. The positivity rate was lowest in this group (0.76%). (Table 2). 74(51%)were on exclusive breast feeding. Positivity was higher in breast feeding (8.1%) and mixed feeding (50%) groups. (Table 3). 5(5.52%) babies were positive in the age group 6 weeks to 6 month. All negative status children remained negative throughout testing protocol (Table 4). One death observed and 12(8.27%) lost to follow up (Table 5)

Table 1: Age of infants at first visit for EID (n=145)

Age groups	Frequency	Percent (%)
6 week-6m	117	80.7
6m-12m	25	17.2
12m-18m	3	2.1
total	145	100.0

Table 2: Type of ARV prophylaxis and Positivity (n=145)

Type of prophylaxis	Frequency (%)	HIV positive	Positivity rate%
Mother +baby	130 (89.65)	1	0.76
Mother+ no drug to baby	8 (5.52)	3	37.5
No prophylaxis to both	7 (4.83)	4	57.14
Baby only	0	0	0
Total	145 (100)	8	5.5

Table 3: Feeding options and Positivity (n=145)

Feeding Pattern	Number		Positive	
	No	%	No	%
Exclusive Breast Feeding	74	51.03	6	8.1
Replacement	69	47.59	1	1.44
Mixed	2	1.38	1	50
Total	145	100	8	100

Table 4: EID results at different stages of testing (n=145)

Age group	HIV Status		Total
	Positive	Negative	
6 week-6month	5(4.27%)	112(95.7%)	117
6-12month	2(8%)	23(92%)	25
12-18 month	1(33.33%)	2(66.6%)	3
Total	8(5.51%)	137	145

Chi square = 5.096 p value =0.078 DF = 2

Table 5: Follow-up of DBS reactive infants/children (n=145)

Reactive	Non eactive	On ART	On CPT	Death	Lost – follow up
8 (5.51%)	137 (94.48%)	8 (5.51%)	131 (90.3%)	1 (0.68%)	12 (8.27%)

Discussion

In India perinatal transmission accounts for 7% of total HIV load. [7, 8]. HIV can be transmitted from a mother to her child during pregnancy, at child birth and through breastfeeding. Almost all infections in infants can be avoided by timely delivery of known, effective interventions to prevent mother to child transmission. HIV infection follows a more aggressive course among infants and children than among adults. Without access to life saving drugs (antiretroviral therapy and cotrimoxazole prophylaxix) about one third of infants die by age 1 year and 50% by age 2 years. Moreover the asymptomatics, below 18 months are missed out on prevention and treatment [4]

Standard HIV antibody testing done in adults cannot identify infected infants in their first year of life due to maternal antibodies which are transferred to the baby during pregnancy [5] Hence This requires a virological test for diagniosing infants. Virological testing detects HIV DNA/RNA.HIV DNA testing can also be reliably performed on specimens collected onto filter paper dried blood spots. The DBS specimens can easily be stored and transferred without cold chain systems to centralised locations for analysis. This is more useful in resource limited settings [9]. The perinatal transmission in our study was 5.51% which is near to WHO 2010 recommendations which aimed to reduce the risk of maternal to child transmission (MTCT) to less than 5%.We are striving hard to reach the zero target. In our study 117(80.7%) of the babies came between age 6 weeks to 6 months with mean age 3.46 months, 25(17.2%) between 6 to 12 months and 3 (2.1%) beyond 12 and upto 18 months. This is consistent with other studies [10, 14].

ART/ARV prophylaxix is a vital component of PPTCT and can potentially reduce the transmission risk to lower than 5% or even lower, if started early in pregnancy and continued throughout breast feeding period [15, 16]. We found that mother-baby pair who received ART/ARV, transmission rate was lowest (0.76%) as compared other groups.

These mothers were regularly visiting the PPTCT clinic during antenatal period, were on efficacious ART regimes (Tenofovir+ Lamivudine+ Efavirenaz) and had institutional delivery. The higher transmission rate in other groups was either mother or baby or neither of them received ART/ARV prophylaxis. The reason being home deliveries, direct walk in deliveries or later diagnosis [10, 12, 13, 17].

Breast feeding have additional 10%-20% transmission risk, which can b lowered down to 1%-2% with replacement feeding and ART regimes during breastfeeding. Benefits of breastfeeding outweighs the risk of mortalities, in early infancy, due to infectious diseases and malnutrition in the absence of breastfeeding. WHO therefore recommends EBF for first 6 months [18]. RBF should be opted only when it is acceptable, feasible, affordable, sustainable and safe AFASS [10].

In our study(51%)mothers adopted replacement(RBF) feeding option, 75% practiced exclusive breast feeding(EBF) and unfortunately two mothers opted mixed feeding inspite of good counseling. The transmission rate was lowest (1.44%) in RBF group as compared to other groups [10, 12, 13, 17].

Effectiveness of EID results can be judged by its correlation with the results at 6 month 12 month and 18 month. We found 5 positive between 6 weeks-6 month group, 2 positive in 6-12 month age group and 1 in 12-18 month group. Out of 145 infants/children 8 were HIV positive and were referred to ART centre for ART initiation and further management. Remaining 137 consistently showed negative status in subsequent testing schedule.

In our study only 2 positive children had completed the 18 month testing protocol. On final antibody testing they found to be HIV positive. 5 are still under follow up and are waiting for 18 month testing shedule. Since all remaining children showed negative status throughout testings, this reflects a good correlation between EID status at first contact and at 6, 12 and 18 months. The EID thus establishes its integrity [10, 19].

All 8 children are on ART while 132 are on CPT. Parent of one child denied to continue with CPT (Reported to ART centre and MP SACS). 1 died within 3 months of life due to sickness and AIDS related symptoms. This child could not get sdNvp until 6 weeks after birth. Lost to follow up is the biggest challenge in combating pediatric HIV. In our study 12 lost to follow up. They could not be traced owing to non availability on their residential address /contact number. Hence it was not ensured whether these children were lost to life or lost to follow up. Other studies reported 16.5% and 67% babies lost to follow up [10, 20].

Study Limitation

Present study is based on the observation of only 145 children and is a part of ongoing intervention, therefore this needs concise interpretation. Lost to follow up was another challenge to arrive on final diagnosis.

Conclusion

The ultimate aim of PPTCT programme is to achieve zero prevalence. MTCT of HIV is the biggest challenge of HIV/AIDS pandemic especially in resource constrained settings Findings in our study demonstrate that reduction in MTCT of HIV is possible with efficacious ART, appropriate infant feeding practices and most importantly early diagnosis. EID helps in diagnosis as early as 6 weeks, ART initiation, assists in decision making on infant feeding and confers an accurate and consistent results throughout the testing protocol. It also provides an unique opportunity for evaluating the success of PPTCT program.

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