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# Early infant diagnosis and post-exposure prophylaxis for HIV- exposed infants

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## *Abstract*

*Recent scientific evidence suggests that early initiation of antiretroviral therapy (ART) among infants exposed perinatally to HIV has beneficial effects on their health and survival, and may even induce remission. This has led to the roll-out of early infant diagnosis (EID) of HIV and early treatment. Also, there is talk of using ART as post-exposure prophylaxis (PEP) to prevent mother-to-child transmission. EID involves carrying out diagnostic tests before initiating ART. In India, current programme design of centralised diagnosis has been resulting in poor access to diagnosis and treatment. To save the lives of HIV-infected infants, it is important to prevent delay. Another issue to be kept in mind is that the results of HIV tests may turn negative after the initiation of ART. This could be due to viral remission induced by ART or false-positive initial results. Differentiating between the two is difficult. To deal with such cases, we need to develop a clinical algorithm*

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*and tools for capacity-building in counselling. The use of ART as PEP is expected to encounter further challenges. Between ART as PEP and EID, the later has advantages from an ethical perspective. There is a need to address the ethical issues within the EID programme by strengthening the current mechanisms for protecting the rights of HIV-exposed infants.*

## Background

The global response to the HIV pandemic has resulted in a decline in the perinatal transmission of HIV to infants, and the introduction of antiretroviral therapy (ART) has also improved the survival of HIV-infected children. However, nearly 200,000 new infections were estimated to have occurred during 2013 (1). This calls for further strengthening of interventions for the prevention of mother-to-child transmission (PMTCT), as well as the provision of care and treatment to those infants who are found to be infected. Recent advances in clinical research offer hope of a functional cure or remission from the infection. An early diagnosis of HIV among infants and the early initiation of ART have been found to improve child survival (2,3) and have been implemented as an intervention across many countries, including India.

Many researchers worldwide have been seeking a cure for HIV infection but none of the attempts has been successful so far. There was much enthusiasm when the Mississippi baby remained negative for blood HIV-1 virus load (The blood HIV virus load test is a sensitive test in which a positive result provides evidence of a number of viruses (HIV) in the blood, and a negative test means absence of HIV in the blood) even after ART was interrupted for 12 months (4). This baby had acquired HIV-1 infection perinatally and ART had been initiated on day 2. However, after 27 months of interruption, this baby had detectable viraemia in the blood and hopes of a functional cure were dashed (5). Nevertheless, it provided proof-of-concept that HIV remission can occur with early ART. There is growing evidence that very early treatment in perinatal infection is likely to be useful in achieving virological remission (6–8). In a few recent studies, researchers have attempted to initiate ART among HIV-exposed children soon after birth (without waiting to confirm the diagnosis of HIV) and have tested the hypothesis that ART as post-exposure prophylaxis (ART-PEP) will eradicate the virus or at least, lead to a functional cure. While early infant diagnosis (EID) is already being implemented across the globe, ART-PEP is an intervention that is likely to be introduced in the near future (9). The ethical challenges involved in research on a functional cure and remission have been commented upon previously (10–13). This paper discusses the ethical implications of today's EID programmes and the possible ART-PEP programmes that can be initiated in the future in India.

## Perinatally acquired HIV in India

India has been implementing prevention of parent-to-child transmission (PPTCT) interventions through its National AIDS Control Programme (NACP) since 2002 (14). PPTCT aims to reduce the transmission of the virus from an infected mother to her baby by providing antiretroviral (ARV) prophylaxis to mother and baby. Initially, ARV prophylaxis included the administration of a single dose of nevirapine to the mother and the newborn and since 2012 a multidrug prophylactic regimen has been introduced in a phased manner. In 2013–14, about 12,000 pregnant women were found to be HIV-positive; 10,085 (84%) of these mothers and their babies received ARV prophylaxis (14).

### *The EID programme:*

EID was introduced in India in a phased manner starting from 2010 (14). The EID programme includes testing infants and children at six weeks, six months and 12 months, and there is an additional test six weeks after breastfeeding has been stopped among breastfed infants. India has a network of 1157 Integrated Counselling and Testing Centres (ICTCs) and 207 ART centres, where blood samples are collected from these HIV-exposed children. Serological tests cannot be carried out because they fail to differentiate between the antibodies produced by the infant and those acquired from the mother. Hence, these samples are then transported to one of the seven regional laboratories (centralised) where the DNA PCR (qualitative) test is conducted. The results are dispatched to the respective ICTCs and ART centres, which communicate the results to the caregivers. For infants whose first sample shows the presence of HIV, a second sample is collected and sent to the regional laboratory for confirmation. In the case of discordant results, a third sample is drawn to determine the child's HIV status. ART is initiated among infants diagnosed in this manner, irrespective of their clinical and immunological status. Since most infants are being breastfed, they continue to be at risk of contracting infection after birth. The HIV status of all HIV-exposed children is finally confirmed at the age of 18 months (maternal antibodies disappear by this time) through three rapid serological tests at ICTCs (decentralised).

## EID: ethical considerations

EID involves testing the blood of infants for the presence of HIV DNA or RNA. Since EID is basically a screening test, it must be justified by the basic ethical principles of beneficence and non-maleficence. Beneficence and non-maleficence can be assessed by applying Wilson and Jungner's principles (20) and more specifically, Clayton's criteria for neonatal screening (Box 1) (21). Perinatally acquired HIV meets all of Clayton's criteria for the screening of newborns. EID as an intervention is ethically justifiable.

**Box 1: Clayton's factors for neonatal screening**

The disease has a devastating outcome.

The treatment is highly effective in averting this outcome, but only if it is started early.

Affected children cannot be detected on the basis of symptoms in time to start effective treatment.

Screening reliably detects the infection in most affected children.

*Source: Clayton EW. Genetic testing and screening: newborn genetic screening In: Post SG (ed). Encyclopedia of Bioethics, 3rd ed. Macmillan; 2004.*

However, there are two issues that need to be considered with respect to the implementation of EID. The first relates to "access", which is integral to the principle of justice. An adequate laboratory infrastructure is needed for the DNA PCR test. For this reason, it is being offered in a centralised manner. However, this model of service delivery creates delays in the health system, including delays in the transport of samples to the regional laboratory, delays in testing at the regional laboratory due to the high load, delays in the communication of the results to the ICTCs and ART centres, and delays in the communication of the results to the caregivers. Studies in sub-Saharan Africa have documented delays in communicating the result of the test to the caregivers, and also, the fact that many infants have dropped out of the EID programme (22–24). A recent report from Tamil Nadu also highlights delays in the health system (a median delay of more than six weeks from the time of the collection of the sample to the time of the communication of the result to the caregivers) under India's EID programme (25). The report also found that nearly one-third of those whose first sample was positive for HIV did not come back to the health system for a confirmation of the diagnosis. The centralised programme design is destined to fail, compound the problem of stigma and discrimination, and result in poor access to treatment.

Under the EID programme, an infant is started on ART if two DNA PCR results are positive. There have been cases in which HIV test results (serological or virological) have turned negative subsequent to the initiation of ART. This discordance may be because of the remission of the virus (26), but may also reflect that the initial DNA PCR test results were false-positive. Thus, clinicians and counsellors may remain in doubt about the HIV-positive status of an infant. There are no operational guidelines on how to differentiate between a remission induced by ART and a false-positive initial test result (discussed in the next paragraph). The current counselling guidelines do not equip counsellors to deal with this complex situation.

The World Health Organisation (WHO) has recommended DNA PCR for the diagnosis of HIV among infants. The test has a high positive predictive value (PPV) in scenarios with high transmission rates in research settings. Limited published data are available on PPV in programme settings. Data from Tamil Nadu show a false-positivity rate of 5% (8 in 164), whereas a study in Malawi reported a rate of nearly 15% (15 in 103) false-positives with a single test. Discordant results have also been reported from Kenya (25,27,28). There are no published data from India on the false-positivity rate after two tests, though recent case reports have provided evidence that false-positive results are indeed obtained after two tests (29,30). Further to this, the declining probability of perinatal transmission due to better PMTCT regimens is expected to affect the PPV of the DNA PCR test adversely; a PPV of 62.5% is predicted if the transmission rate dips to 1% (31,32). This may result in a higher number of false-positive cases, with the subsequent initiation of unnecessary ART. This is likely to not only cause the infant to suffer the physical adverse effects of ART, but also increase the psychological and social discomfort arising from the stigma and discrimination associated with HIV infection.

The clinical management options in such discordant cases would be to continue treatment (risk of harm to non-infected children) or discontinue treatment (risk of harm to infected children due to the emergence of drug resistance). One may propose that these risks should be communicated to the caregiver during pre-test counselling and the choice (autonomy) should be left to the caregiver. Another point to be noted is that the low literacy levels of the caregivers and the social adversities faced by them would make it much more difficult for them to comprehend the meaning of discordant test results during the course of the treatment.

## Addressing challenges posed in the EID programme

To address delays in the health system, it is crucial to adopt an approach of decentralisation as it will reduce the drop-out rate of HIV-exposed children. To retain children under the programme, there is a need to develop a point-of-care test. As for the reliability of the test that is being used, it is difficult to determine whether the failure to detect HIV has been due to a false-positive result or remission induced by ART. The discontinuation of treatment is not ethically justifiable as it may lead to a viral rebound, resulting in a poor outcome for the baby. Treatment could be stopped if there is no other evidence of infection and if serious adverse events are threatening the growth and development of the child. The treatment may get interrupted for other reasons as well, such as if the caregiver does not return to the programme, or there is a shortage of drugs in the health system. In such cases, routine follow-up of the child will be necessary and ART should be re-introduced only if there is evidence of infection. However, this clinical algorithm must be debated upon and national guidelines need to be developed to assist clinical decision-making in discordant cases. Another way to address the issue is to reduce the possibility of false-positives by using the RNA PCR test for the confirmation of the diagnosis before initiating ART (32). At present, ICTC counsellors are responsible for explaining the risks and benefits of treatment, and the meaning of positive, negative or indeterminate test results to caregivers. It is crucial to train counsellors in the clinical algorithm for discordant cases. It is equally important to enhance their counselling skills to meet the needs of caregivers.

## ART-PEP: ethical considerations

PEP is administered routinely, especially to healthcare providers who have been exposed to HIV. By definition, PEP includes PMTCT but it has not involved ART for neonates so far. Recent proposals to improve the survival of HIV-exposed children include the use of ART as PEP for these children (9). If implemented, such a PEP programme will offer ART to all HIV-exposed children instead of waiting for a confirmation of the diagnosis. Is it ethically justifiable to include ART as PEP among neonates?

Four major issues could emerge from PEP. The first is that of limited beneficence. Considering that PMTCT interventions have reduced the risk of transmission to about 7%, even in resource-poor settings, the continuation of ART for a longer duration offers little scope of an incremental benefit. Should ART as PEP then be offered to all? The second issue is related to non-maleficence. On the one hand, children who are born uninfected are at risk of suffering adverse effects due to unnecessary ART. On the other, infected neonates may develop drug resistance after PEP is withdrawn. The third issue pertains to the delay in diagnosis. There is evidence of the induction of remission due to ART, which affects the sensitivity of the DNA PCR test adversely (26, 33, 34), resulting in a delay in the diagnosis of HIV infection. The fourth issue relates to continued exposure to HIV through breast milk. Many HIV-positive women in the lower middle-income countries breastfeed their babies. Besides, the NACP advocates exclusive breastfeeding till six months. This means that ART, although offered as PEP, will be acting as pre-exposure prophylaxis for children who are born uninfected. It is difficult to justify stopping PEP before stopping breastfeeding, especially when the risks and benefits of long-duration pre-exposure prophylaxis among infants are uncertain.

### *Consent*

ART-PEP may be in conflict with the ethically-valued principles of autonomy and consent because the process of informed consent itself will be challenging. First, the issue is so complex that caregivers may find it difficult to comprehend it and make an informed decision. Second, the caregiver (usually the mother) will have to be informed about PEP during or before the delivery and there may not be sufficient time to take a decision. Giving consent during the delivery will create an additional burden on the woman who may have been diagnosed with HIV during labour, and her ability to understand and take a decision may be compromised. This calls for the standardisation of procedures and building of the skills of counsellors. Further, it calls for an improvement in antenatal care so that HIV is diagnosed much before the delivery. It is also possible that PEP may be confused with treatment, resulting in stigma and discrimination against the vulnerable neonate.

### *Addressing challenges posed by ART as PEP*

Evidence of the effectiveness of PEP even among adults is limited (35). Considering the absence of strong evidence on its safety and efficacy, the possibility that it has little incremental benefit at the population level and the several ethical issues that may arise during the implementation of PEP as a programme, PEP should not be introduced as a programme till the results of relevant clinical studies are available. Even thereafter, PEP should be reserved for those who are at high risk of acquiring HIV infection perinatally to minimise exposing non-infected neonates to the adverse effects of ART. Guidelines on the criteria for "at high risk neonate" need to be developed and challenged, and a consensus statement should be arrived at. This consensus statement should also discuss the ethical issues involved in administering ART before a confirmation of the diagnosis. To minimise the risks associated with the adverse effects of ART and with drug resistance, the early diagnosis of HIV infection is important and follow-up of infants till 18 months of age is crucial. This is a difficult task, given the context of stigma, discrimination and high drop-out rates. PEP should be offered only after careful consideration of the willingness to adhere to the treatment and follow-up schedule. No decision should be taken to continue the treatment till the end of breastfeeding till data are available on the safety and efficacy of the same. It must be noted that the success of the current PMTCT regimens in reducing transmission rates almost rules out the need for such clinical research.

The ethical challenges discussed here are not entirely new, but the problem of delay in diagnosis and the ethical dilemma caused by discordant results are new issues. Delay in the diagnosis of HIV infection, resulting in poor outcomes among HIV-infected infants, is an important concern under the EID programme. The centralised design of the programme creates a barrier to access. The use of ART as PEP would prevent this delay, but raise several ethical questions. Improving the efficiency of EID programmes could be an immediate solution, while the development of a point-of-care diagnostic test could be a solution for the future. Reducing the time taken to diagnose HIV infection would eliminate the need for empirical treatment. While remission of HIV is a significant achievement in the fight against the infection, it has raised certain ethical challenges for EID programmes. The programme's data need to be analysed to measure and document the current levels of discordance (negative HIV test results while on ART). There is a need to develop clinical algorithms and strengthen counselling skills to deal with the discordance.

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