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Editorial

Early ART in infants may hold secrets for HIV cure

HIV has been accepted as an incurable infection that can be kept under control, however difficult to eliminate. The hope for possible cure has stemmed from the reports of the populations at high risk of infection remaining free of HIV infection in spite of repeated exposures to the virus. A number of host factors associated with lower susceptibility to HIV infection and better control on HIV multiplication have been reported. However, the correlates of protection from HIV infection have eluded the scientific community. This has been a significant barrier in developing effective vaccine to protect against HIV infection. On the contrary, a spectacular success has been achieved in the field of HIV treatment. A large number of drugs in multiple classes based on their mechanisms of action have become available and sustained pressure from civil society and initiatives by international organizations have been successful in taking the free treatment to majority of those who require it.

Anti-retroviral treatment has made it possible for HIV infected persons to lead a normal life by keeping virus multiplication under control for a long time, thus effectively making HIV a chronic disease that can be kept under control by life long treatment. This has been possible due to availability of alternatives as the first line, second line and third line drugs. Although researchers looked for cure, the HIV reservoir in the resting CD4 cells is difficult to eliminate. Different approaches are currently being followed in an attempt to stimulate the infected resting cells and mopping up the resultant virus particles before they have opportunity to infect fresh cells and establish reservoir.

There was a shot in the arm for cure research with the presentation of a case of 'functional cure' by Deborah et al¹ at the Conference on Retroviruses and Opportunistic Infections in Atlanta early this year. A baby born to HIV positive mother was put on the anti-retroviral treatment within 48 h of birth. The positivity status of the baby was confirmed both by DNA-PCR as well as by RNA-PCR. The baby when retested after 18 months of ARV treatment was found to be negative for HIV infection. The baby continued to be negative after withdrawal of ARV treatment. The investigators claimed a "functional cure" in the baby. This finding was very significant as this functional cure was achieved by administering first line ARV drugs, AZT, lamivudine and nevirapine, which are part of the first line treatment for HIV infection throughout the world.

This may make it a feasible strategy for functional cure. With this report further impetus was given to the research for cure from HIV infection.

In this issue, Mathai et al report a possible cure in an infant born to HIV positive mother.² The infant was diagnosed to be HIV infected based on DNA-PCR for HIV-1. The test was performed in a private diagnostic laboratory accredited by National Accreditation Board for Testing and Calibration Laboratories (NABL). The results were confirmed by repeat testing. At 18 months the baby was tested for HIV-1 antibodies and was found to be negative. The negative status was confirmed by DNA-PCR, repeat ELISA for antibodies and quantitative RNA-PCR. The authors have considered a possibility of elimination of virus as a result of ARV treatment.

These findings raise the issue related to early control of HIV multiplication. A short period of 5–7 days after the exposure to HIV is called an "Eclipse phase" during which there is no virus detectable in circulation. This period may also be very important in deciding whether the immune responses will limit the infection. By the time the virus appears in the blood it may have already spread to different parts of body and established in the lymphoid tissue. Once the virus is established in the lymphoid tissue it is difficult to eliminate the virus. Deborah et al¹ initiated the anti-retroviral treatment within 48 h of diagnosis and may have prevented establishment of the HIV reservoir in the lymphoid tissues. Mathai et al² have initiated the treatment after eclipse phase was over and hence it will be difficult to explain how established infection was eliminated. In "Visconti Cohort", recently infected patients were treated with ART as late as 10 weeks after infection. The treatment was stopped after upto 36 months of treatment. After the treatment was withdrawn the patients continued to have no detectable virus load. The investigators called these as "post-treatment controllers" Sáez-Cirión et al.³ A recent report by Scott G et al⁴ has demonstrated that lentiviral reservoirs that are refractory to ARV drugs may be susceptible to the continuous effector memory T-cell-mediated immune surveillance. Rhesus macaques immunized with RhCMV/SIV vector were challenged with highly pathogenic lentivirus strain SIVmac239. The challenge virus was eliminated even after lymphatic and haematogenous viral dissemination, and persistence of replication competent SIV in several sites for weeks to months

in the immunized monkeys. These evidences suggest that an immune response generated by a vaccine or post-treatment control of virus may eliminate HIV reservoir. Hence the claim by Mathai et al² cannot be dismissed merely on technical context. It is possible that along with ART the immune response of the baby may have eventually helped in clearing virus reservoir. The Authors themselves have been cautious in their interpretation and have not ruled out false positive results in DNA–PCR.

Although the two cases are similar, there are distinct differences in the two reports. While the infant was put on anti-retroviral treatment within 48 h in the Johns Hopkins study the infant in study by Mathai et al was put on the anti-retroviral treatment after 6 weeks. One of the limitations brought out by the investigators is that the diagnosis in the infant was not confirmed by RNA–PCR. The DNA–PCR, with low population prevalence, is likely to be false positive as the positive predictive value of the test dips significantly in populations with low prevalence. The Department of AIDS Control, Government of India has implemented early infant diagnosis programme that depends heavily on the DNA–PCR for diagnosis of HIV infection. Presently there are no clear guidelines or algorithms for diagnosis of HIV infection among children born to HIV infected persons. With very low population prevalence rates, reconsideration may be needed for test algorithm for diagnosing HIV infected infants. Also, attempts need to be made for diagnosis in the infant as early as possible, to provide a chance for early treatment. There is need for parallel attempts to build infra-structure to make a reliable diagnosis of HIV infection in children born to HIV infected mothers by including RNA–PCR in the algorithm.

World Health Organization (WHO)⁵ has recently released the new guidelines for treatment of HIV infection. As per new guidelines all children below 36 months are recommended to be put on Lopinavir/Ritonavir based regimens. If the findings

reported by Deborah et al¹ and Mathai et al² are further confirmed in larger clinical studies, the new WHO guidelines would probably pave way for AIDS free next generation. Hence these findings are extremely significant and need to be followed by larger and controlled studies. The paper will indeed generate discussion on this important advancement.²

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Ramesh S. Paranjape
Director, National AIDS Research Institute (ICMR), Pune, India
E-mail address: rparanjape@nariindia.org

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