Immediate access to antiretroviral therapy is important in children living with HIV

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Abstract

This article reviews a case of a child with perinatal HIV followed for 30 months during a prospective cohort study on pneumonia prevention in HIV-infected children. The point of this case report is to illustrate how delayed access to antiretroviral therapy (ART) in HIV-infected children impacts immunization response and growth. Given the WHO’s early release guideline changes on ART recommendations and the expected full revised guidelines coming out this year, this article is a timely discussion on the need for access to ART for HIV infected Indian children regardless of CD4 count.

Keywords: Access, antiretroviral therapy, HIV, immune response, vaccines

Introduction

The child described in the case history given below was followed during a prospective cohort study to look at the impact of the Haemophilus influenzae type b conjugate vaccine (HibCV) and pneumococcal conjugate vaccines (PCVs) in children and their families living with HIV infection. This clinical summary underlines a need to consider the importance of access to antiretroviral therapy (ART) in HIV-infected children regardless of CD4 count.

Case Report

A 4-year-old boy with perinatal HIV was enrolled in a prospective cohort study in March 2012. At study entry, this child had already gotten three doses of HibCV in infancy through a private provider. At enrollment in March 2012, he had a CD4 count of 753 cells/mm³ and was not on highly active ART (HAART) but was on trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis. The plasma viral load was found to be 251,000 copies/mL. His weight for age Z-score was −2.25, and his height for age Z-score was −2.07. A baseline blood test for anti-Hib PRP antibody showed a level of 0.35 µg/ml meaning that he was susceptible to H. influenzae type b (Hib) infections despite being immunized in infancy. As a part of the study, children received two doses of HibCV and one dose of the 13-valent PCV and were followed for nasopharyngeal carriage at multiple time points over the course of the study, for 30 months. He had nasopharyngeal carriage with Hib, and the isolate was TMP/SMX resistant. His CD4 count dropped to as low as 440 by study end in September 2014. He still did not qualify for ART because his CD4 count had not dropped to 350 cells/mm³.

Discussion

HIV infection destroys both cellular and humoral immunity. Early on, before T-cell depletion is evident, antigen-specific memory B-cells disappear, and there is a loss of specific antibody obtained through routine childhood immunizations. A study in an Italian cohort of vertically infected children, who had received measles vaccine in infancy, demonstrated that children introduced to ART early, in the 1st year of life, had an immune response to measles vaccine 10 years after immunization which was comparable to that of an Italian cohort of perinatally infected children who had received measles vaccine in infancy, but who had not received ART early. This study highlights the importance of immediate access to ART in children living with HIV.
uninfected control children.[3] In contrast to this, the majority of HIV-infected children, who had late HAART introduction or were untreated, did not have protective measles antibody titers. Furthermore, children with late access to HAART, even when they were revaccinated did not mount as robust an immune response, as children with early access to HAART. Early access to HAART preserves memory B-cells.[2]

Nadir CD4 counts predict immune response to vaccines even after starting HAART. In a study in HIV-infected individuals on HAART with immune reconstitution and controlled viral replication, nadir or the lowest pretreatment CD4 count, not current immune state, predicted the ability to respond to standard vaccines.[3] In HIV-infected children nadir CD4 count was a predictor for the PCV to confer memory; children with higher nadir CD4 counts were more likely to have a fourfold antibody rise following a PCV booster.[4]

Another important factor in determining immune response to vaccines in children with perinatal HIV infection is the percentage of life spent with undetectable viral load.[8] HIV infection has profound effects on the developing immune system. Unlike in adults where viremia decreases in the weeks following infection, children are unable to contain viral replication and untreated have unchecked viral loads reaching >100,000 copies/ml and can reach over a million copies/ml. Chronic HIV viremia leads to a situation of clonal expansion of HIV-specific T cells and the inability of another pathogen-specific effector and memory T-cells to develop. What this means is fewer T-cells are available to become antigen-specific effector and memory T-cells following routine immunizations.[8] Similarly, uncontrolled HIV viremia leads to nonspecific activation of B-cells, hypergammaglobulinemia, and apoptosis or death of memory B-cells all resulting in an inability to respond appropriately to an antigenic challenge such as a vaccine.[8]

Immediate access to HAART is of paramount importance in HIV-infected individuals particularly children. Early on, the virus invades peripheral blood mononuclear cells (PBMC) and hides out remaining latent, evading detection from the immune system and forming a reservoir in resting memory CD4 T-cells.[1] Proviral reservoir stores in PBMC determine long-term remission. A cohort study in perinatally infected children showed that children who had virological control by age 1 had a median of 4.2 proviral copies/1 million PBMC compared to those with virological control after age five who had a median of 70.7 proviral copies per million PBMC.[1] Children with lower proviral loads were more likely to have an HIV indeterminate status in adolescence. What this means is that early access to combination ART and prolonged virological control is critical to long-term remission in perinatally infected children.

The INSIGHT START study published in August 2015 showed that HIV-infected individuals started on HAART immediately, instead of deferring till CD4 count dropped to ≤350 cells/mm³ had a 57% decreased risk of death, AIDS-related serious events, and non-AIDS related serious events.[8] This randomized controlled trial was carried out in nearly 5000 HIV-infected adults in 25 countries. The median viral load in adults in this study was 12,759 copies/mL far lower than viral loads expected in untreated children. As a result of this study, the WHO issued revised early release guidelines in September 2015 which say that “ART should be initiated in everyone living with HIV at any CD4 cell count.”[8]

The 2013 National AIDS Control Organization guideline make ART available to HIV-infected children over five only when their CD4 count drops <350 cells/mm³. In contrast, Sri Lanka, Bhutan, and Bangladesh have guidelines that provide ART for children over 5 years for CD4 count <500 cells/mm³. In children not only does untreated HIV lead to unusual problems in the immune system but also it affects other critical parameters such as growth as in the case described above. Untreated HIV-infected children are more likely to be stunted and do not catch up to full adult height potential after delayed treatment.[8] It is time for Indian guidelines for pediatric HIV to reflect the changes in global thinking and make ART available to children regardless of CD4 count.

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Conflicts of interest
There are no conflicts of interest.

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