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Apparent Viral Clearance in HIV-Infected Children on Antiretroviral Therapy (ART) is Possible

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Abstract

Background: Temporary clearance of HIV- antibodies (Ab) and -antigens (Ag) in the serum of HIV-infected children on effective antiretroviral therapy (ART)-regimens with excellent adherence are occurred occasionally. However, it is unlikely that ART alone can lead to HIV remission or cure due to rapid formation of persistent viral reservoirs follows acute HIV-1 infection.

Case Series: We report a case series of three young patients attending the ART-clinic of Asella Teaching Hospital (ATH), Arsi Zone, central Ethiopia, in which ART has been stopped due to the negativity of serum antibodies and antigen-essays. This turned out to be a mistake as all children experienced a rebound of viral load (VL) within a few months after stopping ART.

Discussion: In our patients, even with apparent clearance of the virus, HIV was not eradicated. This must remind treating physicians that clearance of serum HIV-antigens and antibodies in children on ART does not mean a cure of the HIV-infection and it frequently only represents a temporary status. If ART is stopped, the child should be continuously monitored, as a rebound of VL in the short term is highly probable. The combination antiretroviral therapy (cART) can reduce HIV viral loads to undetectable levels due to the host gains excellent immunity status. Because of some latently infected CD4+ T-cells represent a major reservoir of HIV that persists during cART, the infection can rapidly reemerge if the treatment is discontinued.

Conclusions: From these series case reports, we can conclude that there could be possibility of temporarily viral clearance and seronegative conversion in children on effective ART does not mean a 'cure' of the HIV-infection. If ART was stopped due to high suspicion of the "first positive result" following antibody and antigen negative test results after 18 months, the child should be strictly and continuously monitored. Rebound of plasm VL within short term is highly probable. In defaulter patient, viral re-supersession with reinitiating same ATR- regimen is possible.

Keywords: HIV; Children; Antiretroviral therapy

Introduction

Temporary clearance of HIV- antibodies (Ab) and -antigens (Ag) in the serum of HIV-infected children on effective ART-regimens has already been described in the literature [1,2]. However, it is unlikely that ART alone can lead to HIV remission or permanent clearance of HIV-Ags from the serum of the children due to rapid formation of persistent viral reservoirs follows acute HIV-1 infection [3]. This early establishment of latently HIV-1-infected CD4+ T-cells harboring replication-competent virus remains the major obstacle to HIV cure or remission [4]. ART, even when given within days of infection, usually fails to clear these reservoirs [5,6].

In resource limited settings, the clinical phenomena such as successfully suppressed plasma viremia for prolonged periods of time and non-reactive of HIV-Abs could be considered by healthcare workers (HCWs) working at HIV-care and treatment clinic as "cured" leading to discontinuation of ART-regimens and discharging the patient from follow up schedule. Despite such extraordinary successes unless HIV-infected individuals who are receiving clinically effective ART remain on continuous and uninterrupted therapy for their whole lives, rapid plasma viral rebound will be observed with short times [7].

ATH is the second referral and teaching hospital in the Oromia region, Ethiopia and serves about 4 million people in its catchment population. Hirsch Institute of Tropical Medicine (HITM) is an institute working in close collaboration with the College of Health Sciences and ATH. The overarching goal is a long-term collaboration between Heinrich Heine University in Germany and the Arsi University in Ethiopia. ATH has a separated HIV clinic, which is delivering HIV-care and treatment for patients living with HIV/AIDS. A total number of A5938 people living with HIV/AIDS were enrolled in the care and treatment and on follow up. Currently, 3479 are on ART, from which 38.9% of them were males and 8.4 % of them were children age less than 15 years. From 3,479 on ART, only 5.6% of them were on the second line and of these 19.5% (38/195) them children.

We report a case series of three young patients attending the ART-clinic of ATH, Arsi Zone, central Ethiopia, in which ART has been stopped due to the negativity of serum antibodies and antigen-essays. This turned out to be a mistake as all children experienced a rebound of viral load (VL) within a few months after stopping ART.

Case Series

Case-1

A five-year-old female child who was born to a mother with HIV infection was on follow up at HIV-Care and treatment clinic. The child was born through spontaneous vaginal delivery to an HIV infected mother and was started on Nevirapine prophylaxis. The mother opted for exclusive breastfeeding and the infant was on exclusive breastfeeding for five months until the mother died of advanced HIV/AIDS illness. At six weeks of postnatal age, dried blood spot (DBS) was taken for DNA-PCR. The result of DNA-PCR turned to be positive and the infant was started on cART (d4T+3TC+NVP) and co-trimoxazole therapy. The child was adherent to her cART medication and on regular follow up. During follow up evaluation, the child was thriving well and there was no apparent medical complication observed with normal CD4 count.

At the age of five years as the child was asymptomatic and growing well the family requested the test to be repeated for which the child was retested using rapid HIV1/2 antibody test and turned to be negative. Then, the test repeated using DNA-PCR, which again turned to be negative. Because such discordant results were unusual before, a child's blood sample was transported to German for further molecular testing using Western blot. Among all tested HIV-antigens using Western blot, only p25 and p55 were detected while p68, p52, p40, p34, p18, p160, p120 and p 41 were all negative. After a number, discussion with experts in the field the cART was discontinued and decided that the child should be on regular follow up.

Thirty-nine days later after discontinuation of cART, the child was admitted with a diagnosis of pulmonary tuberculosis (PTB) after presented with fever and cough of two weeks duration.

A rapid HIV1/2-antibody-test was performed and found to be positive and viral load was determined and turned to be 64,000 copies/ml. Then, the child was immediately restarted on new ART-regimen (TDF+3TC+EFV). Then the child was remarkably improving clinically and gaining weight (BMI=15 kg/m^2) and CD4 count was 929 cells/mm3) by the time she completed PTB treatment. According to latest follow up visits (March 2109) the clinic, her overall clinical condition was stable and her laboratory updates showed excellent immunological and virological responses (CD4 count=1497 cells/µl and viral load <1000 copies/ml).

Case-2

A female neonate was born to an HIV positive mother through spontaneous vaginal delivery. The mother was diagnosed with HIV infection during the time of labor and delivery. The newborn started on Nevirapine prophylaxis. At six weeks of postnatal age, DBS for DNA-PCR was collected and the result was positive for HIV-infection and the infant started cART. Later the mother had died after she started taking ART for only a month. At the age of 18 months, serologic test for HIV was performed which became negative. DNA-PCR HIV test repeated and found to be negative. Then, the families considered as the child already "cured" and they discontinued the cART and disappeared from follow up. The child was traced from home and brought back to the hospital for further evaluation and we collected and transported the plasma samples to German for further investigations. Both viral load (86,400 copies/ml) and Western blot result clearly indicate that the child is infected with HIV and at the spot, before she restarted on ART, HIV1/2 Abs test was done and became positive. The families were communicated about the result and well counseled and child restarted on antiretroviral drugs (AZT+3TC +LPV). At her last visit (January 2019), she is adherent to her medication, well-looking child, thriving well with normal physical findings. Her laboratory updates are CD4 count=1087 cells/µl and viral load <1000 copies/ml.

Case-3

A female neonate was born to HIV infected mother at home and the neonate brought to the hospital for essential neonatal care where the neonate started on Nevirapine prophylaxis for six weeks. The mother was not on ART but she opted for exclusive breastfeeding from birth. At 6 weeks of postnatal age, DBS for DNA-PCR was taken and became positive. Then, the infant started on ART following national guidelines (AZT+3TC+NVP). The child was taking ART up to the age 4 years at which time antibody for HIV-1/2 test was re-performed, the result was turned to be negative, and PCR from DBS was performed and became negative. In addition, the family disappeared from follow up and by the time the child was contacted, she was off ART for 1 year and 4 months.

The child was traced hence then whole blood and plasma sample was collected and transported to German for further investigations. Both viral load (88,000 copies/ml) and Western blot result clearly indicated the presence of HIV antigen implying that the child remained infected with the HIV virus. At the spot before she restarted on ART, the serologic test was done for HIV1/2 and became positive. Therefore, the child restarted on (TDF+3TC+EFV) antiretroviral drugs. Her latest (March 2019) clinical evaluation finding was normal with laboratory result updates: CD4 count=1216 cells/CD4 percentage=33.8 and viral load <1000 copies/ml.

Discussion

In our patients, even with apparent clearance of the virus, HIV was not eradicated. This must remind treating physicians that clearance of serum HIV-antigens and antibodies in children on ART does not mean a cure of the HIV-infection and it frequently only represents a temporary status. Stopping ART in these children is therefore very risky and must be carefully evaluated. If ART is stopped, the child should be continuously monitored, as a rebound of VL in the short term is highly probable.

Early cART initiation may lead to the absence of HIV-1 antibodies and in a sustained undetectable plasma HIV-1-RNA and proviral-DNA for good adherence patient. HIV-1 antibodies test reverted from positive and could be fully negative after a few years of cART [8]. In these case series reports, probably no enough level of circulating HIV-1, which able to induce specific anti-HIV antibodies due to effective cART. However, as we described in case series reports both HIV antigens and antibodies would be detected if the treatment was stopped. Some latently infected CD4+ T-cells, represent a major reservoir of HIV that persists during cART, the infection can rapidly reemerge [2,9,10]. Calin R. et al. investigated that p25, p55 HIV antigens were detected early [8] by Western blot method similar to case-1 above.

Even though many researchers have exasperated to induce the expression of latent genomes within resting CD4+ T-cells as the primary strategy to clear this reservoir, proviral latency of HIV remains a principal obstacle to curing the infection [11]. The Berlin patient's hematopoietic cell transplant [12], the Mississippi child [13]

and other studies undertaken in various places could be a good examples for the difficulties [1].

ART adherence is low for children in developing countries when compared to adults and to developed country respectively. The unique problems are the dependence on caregiver`s awareness or willing [14,15], national guideline limitations, absence of routine viral load tests and highly qualified experts in the fields, and lack of instruments which can detect latent HIV infections may be a reason to discontinue the ART which leads to treatment failures and multi-drug resistance expansions. Another critical issue for children with virological failure on second-line treatment is the lack of further options for ART and challenge of drug selection due to resistance test rarely done in many developing countries [16]. Thus careful clinical monitoring remains essential to assess the risk of treatment failure among children.

Even though many literatures in case of adults showed us people, who initiated NNRTI-based ART had significantly greater risk of virological failure than ART-naive people [17], we understood from these cases viral re-supersession and gaining CD4 counts is possible when defaulter patient reinitiated same ATR- regimens.

The rapid and very sensitive novel immunoassay, which is recently innovated as result of dual electrophoresis detection system and nanoparticle signal amplification principle, may solve the undetectable level of the virus [18] or the blood may be analyzed with robust, sensitive and specific assays to quantitate reactivatable latent virus [19]. The current treatment approaches to HIV cure or remission have focused on reversing latency or enhancing immune responses [6].

Conclusion

We reported three cases of apparently cured HIV-infected children in ATH. All the three children showed at follow up high viral loads and positivity for HIV-Ab/Ag, meaning they had a highly active HIV infection after they stopped cART. From these case series reports, we can conclude that there could be possibility of temporarily viral clearance and seronegative conversion in children on effective ART does not mean a 'cure' of the HIV-infection. ART in these children should therefore not be stopped. If ART was stopped due to high suspicion of the "first positive result" following antibody and antigen negative test results after 18 months, the child should be strictly and continuously monitored. Rebound of plasm VL within short term is highly probable. In defaulter patient, viral re-supersession with reinitiating same ATR- regimen is possible. Further study is needed to better understand the significance of an undetectable immunoglobulin and cellular HIV reservoir for HIV remission.

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