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Evaluate the changes of clinical markers in HIV-infected pediatric patients treated with antiretroviral therapy at the National Hospital of Pediatrics, Hanoi, Vietnam

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Abstract

Background: According World Health Organization (WHO) guidance on the treatment of HIV infected children, children should be treated with antiretroviral therapy (ART) as soon as they are diagnosed with HIV infection. Even in that case, we found in Vietnam up to 21% of HIV infected children suffer from treatment failure a manifested by reduced immune system and increased HIV viral load (according to WHO criteria). We hypothesized that the ability to response to ART treatment could be related to certain extent with the immune status and clinical markers of HIV infected children.

Aims: To monitor the alteration of clinical, subclinical markers during the course of treatment.

Methods: The study was designed as nested case-control study, we selected all treatment failure (TF) subjects (54 children) and 47 matched treatment success (TS) subjects, the results were analyzed using Chi-squared and non-parametric tests.

Results: The number of CD4 T cells, opportunistic infections and SGPT/ALT levels during treatment were correlated with the ability to respond to treatment in HIV-infected children. In addition, the responders also recoverd better in terms of immunological and other biological markers including hemoglobin, platelets, and liver enzymes than non-responders.

Conclusion: The results showed that improvement of CD4 cell numbers, and reduced levels of liver enzymes SGOT / SGPT can be associated with good response to treatment. Therefore, monitoring these markers during the treatment can be beneficial in prognosis the treatment response.

Keywords: Hiv, Clinical/Subclinical Markers, Treatment Response, Antiretroviral Therapy

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Introduction

In 2015, there were approximately 35 million people living with HIV and 10% of them were perinatal infected children [1]. In Vietnam, there are more than 215,000 people living with HIV, of which over 5,500 are children [2]. Only 4% of the world's population are infected with HIV whereas 20% of the AIDS death are children [3]. Numbers of research has shown the rapid progression of disease among HIV pediatrics especially in developing countries where there is limited access to antiretroviral therapy (ART) and limited resource to monitor the treatment response [3]. The study of Pham et al indicated that after 24 month initiation of ART, up to 21% children suffer from treatment failure, manifested by a decline in immune function and severely reduced general health [4]. Treatment failures are often as consequence of drug resistance and mutations of the HIV virus; once the medical test detecting mutation is not implemented, the patients would consequently lead to treatment failure at higher rate compared to that in developed countries.

Perinatal infected children progress to disease and develop treatment failure more rapidly than infected adults [5, 6]. The ART treatment has shown to successfully control the viral replication, leading to the suppression of viral load to undetectable levels. Beside the ART,

immune system is also considered to be one of the most effective modes to control viral infection. And as the viral load is suppressed, the immune system is believed to be recovered at much more profound rate and is expected to be able to combat against certain types of opportunistic infections. However, as the high rate of treatment failure, these patients must switch to a second line ART with different regimens. And at this time point, children would suffer from decreased immune system and elevated levels of HIV viral load especially the appearance of the mutated virus.

Beside two golden markers to monitor the treatment responses in HIV treated patients including CD4 T cell counts and HIV viral load, other biochemical and hematological markers were also studied in order to monitor the response such as liver enzyme Alanine transaminase (ALT) and Aspartate transaminase (AST), hemoglobin, platelet counts, triglycerides and opportunistic infections. The elevations of ALT and AST are usually found in certain diseases linked to liver abnormality including using epileptic drugs, anti-fungal and treatment with ART. Antiretroviral drugs including protease inhibitor might cause damage to liver cells and hence increase levels of ALT and AST. However, the levels of such elevation are also dependent on other factors including treatment response. Other factors might also be associated with treatment response including blood lipid markers such as serum levels of triglycerides and blood markers including platelet counts.

The study aims at evaluation of the clinical markers including biochemical, immunological, hematological markers such as CD4 T cell counts, viral load, hemoglobin, platelet counts, ALT/AST and opportunistic infections in order to monitor the change of HIV-infected pediatric patients treated with ART and from which to develop the proper recommendation to the clinicians regarding the treatment response of the HIV infected children.

Materials And Methods

Research Design: The study was designed as nested case-control study in which the data was based on the data of the study called "ART treatment for HIV infected children at National Hospital of Pediatrics" [4, 7-9] collected from 2008-2012. The cases and controlled were defined as the following:

Cases (patients suffer from treatment failure or nonresponders): During treatment follow-up, patients had encountered one of these failures: clinical failure (the clinical stage of opportunistic infection is characterized at levels 3-4, according to WHO classification), immunological failure (the levels of CD4 T cells counts were decreased more than 5% of that levels before treatment), or virological failure (HIV viral load was greater than 5,000 copies/ml) [10]. Controls are defined as patients without treatment failure occurred during 36 months of treatment.

The HIV infected children, who had visited and received treatment at the National Hospital of Pediatrics from 2008 to 2012, were included in the study. After 36 month follow- up, a total of 270 HIV infected children was recruited, of which 254 were treated and monitored periodically. After 36 months, 54 pediatric patients were characterized into nonresponders (TF) and 200 were responders (TS). HIV medication, clinical examination and counseling were conducted periodically. Laboratory tests were conducted every 6 months, with the exception of viral load was implemented at least once a year.

Sample sizes:

The study used principle EPV – events per independent variables – in order to calculate the sample size. The event is defined as treatment failure and the independent variables are defined as clinical markers. The EPV principle has been proven to be appropriate for the epidemiological studies using nested-case control study or longitudinal study [11]. According to the principle, the study investigate five independent variables, thus the sample size has calculated to be 100 pediatric patients, including 50 responders and 50 nonresponders. We chose all 54 cases and therefore randomly selected 54 controls among 200 responders. However, in 54 controls, there were 7 controls with insufficient information on blood biochemical, immunological markers so we used 47 remaining controls.

Analysis:

The characteristics of the HIV infected children between the two groups: responders and nonresponders were compared by Chi square test. test at the 5% significance level.

Results

There were total 54 cases and 47 controls included in the study. According to the table 1 there was no significantly different between sex, age and the levels of opportunistic infection of the study.

Characteristics		TF		TS		p (χ^2)
		N	%	N	%	
Sex	Male	12	25,53	22	40,74	0,107
	Female	35	74,47	32	59,26	
Age group	<1	3	6,38	4	7,41	0,778
	1-<5	26	55,32	34	62,96	
	5-<10	16	34,04	15	27,78	
	≥10	2	4,26	1	1,85	
Opportunistic infection	No	16	29,63	9	17,39	0,15
	Yes	38	70,37	38	82,61	

Table 1. The characteristics of the cases and controls
TF: Treatment failure
TS: Treatment success

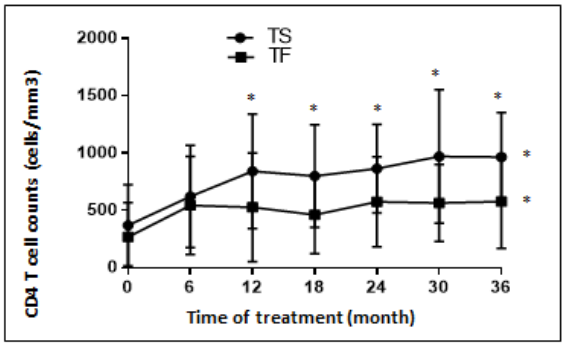

Figure 1. The changes in CD4 during the 36 months of treatment

In figure 1, there was no statistically significant difference in CD4 T cell counts between cases and controls before starting the treatment (p=0.14). However, after the treatment initiation, TS group showed marked increase in CD4 T cell counts and the levels were much more profound than those of TF group. The difference between the two groups was statistically significant (p <0.001).

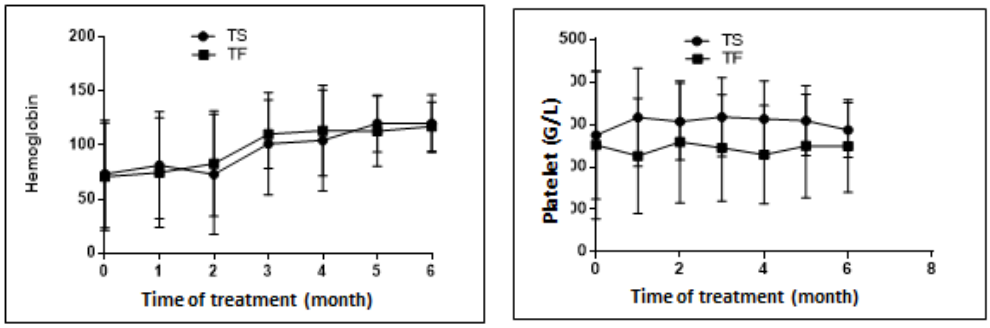

Figure 2. Hemoglobin and platelet levels during the treatment

The hemoglobin levels of both TS and TF groups raised during the course of treatment, even though the different has not reached statistically different. In addition, changes in hemoglobin and platelet levels were not significantly different between TS and TF groups (p = 0.69 and p = 0.8, respectively).

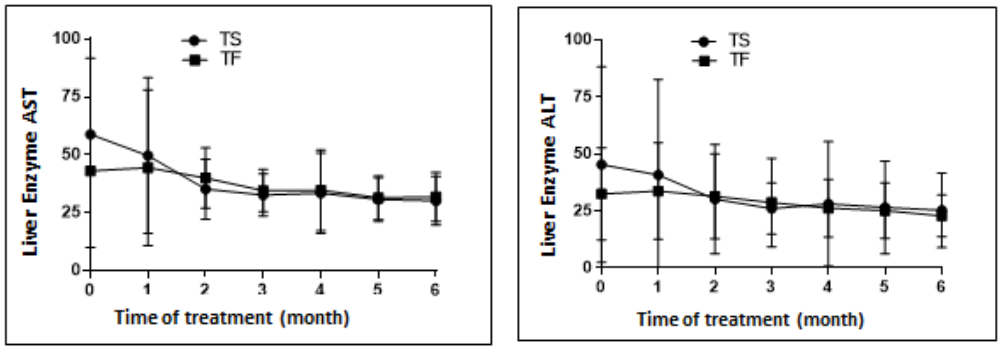

Figure 3. Liver enzyme ALT and AST levels during treatment

It can be shown in figure 3, the AST and ALT levels of TS group decreased rapidly during the first period of treatment (especially at time point 1 and 2, equivalent to 4 and 12 months after starting treatment respectively) compared to those of TF group, however, the different between the two groups at latter time points showed no significantly different (p = 0.84 and p = 0.36, respectively).

Opportunistic infection	TS				TF			
	Before treatment		After treatment		Before treatment		After treatment	
	N	%	N	%	N	%	N	%
Persistent generalized lymphadenopathy	4	12,9	0	0	6	9,0	1	1,8
Unexplained persistent Hepatosplenomegaly	3	9,7	0	0	3	4,0	0	0
Recurrent oral ulceration					2	3,0	1	1,8
Extensive wart virus infection	1	3,2	0	0	9	13,4	13	23,6
Herpes zoster	1	3,2	0	0	1	1,5	1	1,8
Recurrent or chronic upper respiratory tract infections	3	9,7	13	100	13	19,4	25	45,5
Unexplained moderate malnutrition not adequately responding to standard therapy	4	12,9			6	9.0	1	1.8
Unexplained persistent diarrhea (14 days or more)	1	3.2	0	0	4	6.0	0	0
Persistent oral candidiasis (after first 6 weeks of life)	1	3.2	0	0	6	9.0	2	3.6
Pulmonary tuberculosis	5	16.1	0	0	2	3.0	0	0.0
Severe recurrent bacterial pneumonia	1	3.2	0	0	13	19.4	2	3.6
Seborrheic dermatitis	7	22.6	0	0	2	3.0	9	16.4

Table 2. Opportunistic infection in HIV infected children

Table 2 presented the opportunistic infections (OIs) before and after starting ART treatment in two groups TS and TF. In the TS group, the proportion of patients infected with OIs decreased dramatically as well as the stage of OIs significantly decreased from stage 3 to stage 2 according to the WHO classification. On the contrary, in TF group, the prevalence of OIs was not significantly reduced before and after starting treatment. Similarly, the OI of TF group did not decrease as much as that of the TS group.

Discussion

The results showed that among HIV infected children diagnosed and treated with ART for the first time, the children under one year of age accounted for less than 8%, the groups of children from 1-5 years of age accounted for the highest proportion, followed by children from 5-10 years old. The delayed diagnosis and treatment is also consistent with other studies conducted in developing countries such as Senegal, Rwada, India and Africa [12-15]. The delayed diagnosis was found to be correlated to low levels of education, social stigma and limited knowledge on HIV infection [16, 17]. Delayed diagnosis might result in reduced treatment response because of the distorted immune system in these patients. In addition, these children were also co-infected with other opportunistic infection and suffer from certain side-effect of ART related symptoms including anemia, impaired functions of different systems such as kidney, livers etc. HIV infected children in our study also showed such symptoms including anemia, toxic to the liver (manifested by liver enzyme levels), prolonged diarrhea and sleep disorders. It might be suggested that the efficacy of the opportunistic infection treatment might be minimized and the nonresponders were

often unable to eliminate the opportunistic infections after 36 month of treatment. On the contrary, responders were not only able to eliminate the opportunistic infections effectively, but also manage to normalize the levels of liver enzymes and hemoglobin.

The large-scale study called PLATO II and COHERE conducted in 1007 HIV infected children treated with ART showed that there were 5% treatment failure after 5 years followed up, which is much lower than that of developing countries and our study [18]. Using the Cox regression model, the study showed that the age to start treatment was shown to be dependent on the treatment response. However, in our study there was no statistically significant difference between the age to start the treatment between TF and TS groups, nor did we find a statistically significant correlation between age to start treatment and the treatment response (data not shown). The inconsistent between the two studies might be the results of limited number of patients recruited in our study.

The majority of HIV children diagnosed with HIV were infected with other opportunistic infections (70.37% in TS group and 82.61% in TF group). Our data is consistent with the finding reported by Fru et al., in which the number of HIV-infected children with opportunistic infections was 83.5%, and the frequent opportunistic infections include persistent fever, malnutrition, persistent generalized lymphadenopathy, recurrent or chronic upper respiratory tract infection, prolonged diarrhea etc [14]. Other studies based on community indicated that weight loss, prolonged fever, persistent systemic lymphadenopathy, and prolonged diarrhea were the four most prevalent predictors of HIV infection [19]. Most of the HIV infected children were infected with other OIs in clinical stage 2-3 according to the classification of World Health Organization (WHO) classification of HIV/AIDS. However, the clinical stage or the presence of opportunistic infections could not answer the question of whether the children are able to response to ART.

The results showed that there was no statistically significant difference between the CD4 T cell counts and CD4 percentage at baseline between TS and TF groups. Similarly, there was no statistically significant difference of other biochemical markers including hemoglobin, platelet counts and liver enzyme ALT and AST between TS and TF groups. The finding is incompatible with other paper stating that CD4 T cell counts is the most reliable markers in predicting the treatment response in adults [20]. Other studies have also shown that sex, number and percentage of CD4 cells at time T0 and clinical stage of OIs are not statistically correlated to treatment response in infants [20]. Based on the data, we might suggest that the recovery of the body and of the immune system depends on factors other than CD4 counts.

Prior to ART treatment, most patients included in the study had CD4 T-cell counts, hemoglobin levels lower and liver enzymes ALT, AST higher than those in normal children. There was no different between the two groups TS and TF regarding the above values. During the treatment, patients on both groups showed an improvement in terms of physical factors including weight and height, CD4 cell counts, hemoglobin and platelet levels, and liver enzyme levels and HIV viral load. However, the improvement of the two groups was not uniformly similar, in TS groups, the CD4 T cells counts increased up to 468 cells/mm3 whereas, these are 330 cell/mm3 after 36 month of treatment in TF group. Hemoglobin levels also increased in both groups especially in TS group. Similarly, the platelet levels were also increased although the concentration has not reached the reference value. In addition, the TS group reduced the liver enzyme AST to a reference value and the ALT decreased but still higher than the reference values in children. Overall, the TS group could normalize clinical markers better than that of TF group.

The number of CD4 + T-lymphocytes, opportunistic infections or hemoglobin levels were all affected the treatment response of HIV-infected children. Thus, the recovery of the immune system based on treatment might be an important factor in the prognosis the treatment response. Opportunistic infections not only weaken the immune system but also complicate the immune system and the treatment of certain opportunistic infections that may affect the effects of ART. Low hemoglobin, anemia was found to be associated with disease progression, whereas ART can lead to anemia in some patients and anemia caused by ARV may be a mechanism that could be closely related to the response of HIV-infected patients.

Opportunistic infections in HIV-infected pediatric patients were found to be closely related to treatment failure, which may be explained by the fact that the treatment failure is usually associated with a decline in the immune system manifested by decreased CD4 T cell counts. In addition, hemoglobin levels and AST concentrations also might affect the OIs. Yadav J et al. also found a correlation between the severity and the prevalence of opportunistic infection with CD4 cell counts, in which patients with the higher of the CD4 cells also experienced the lower incidence of infectious diseases [21]. In the TS group, the prevalence of OIs decreased significantly in this group, with only few children still acquired certain OIs of clinical stage 2 with mild symptoms such as upper respiratory tract infection. Thus, after treatment, the immune system not only recovers but also is able to combat against the OIs. In consistent with the finding, the study by Jankowska M et al. showed a strong correlation between CD4 cell counts and the incidence of OIs, in addition, up to 45% patients died from OIs including candidiasis, tuberculosis, pneumonia, and nervous system toxoplasmosis [22]. Ghate M et al. also demonstrated that patients with CD4 cell counts below 200 cells/ml were 6 times more likely to be infected with OIs than those with CD4 cells above 350 cells/ml [23, 24]. Other studies with larger scale such as those of Patton L et al found a link between oral-based infections and CD4 cell counts as well as HIV viral load and suggested that this could be a marker for follow-up therapy [25]. The correlation between CD4 T cell count and the incidence of OIs has been found in a large number of papers implemented in both adults and children, as well as in different ethnic groups and geographic locations [21, 26, 27].

Overall, in TS groups, children tend to recover better after the treatment compared to TF groups, thus monitoring the changes in the clinical markers might help to predict treatment response and thus, might help clinicians to develop proper treatment regimen for each individual.

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Compliance with Ethical Standards

Conflict of Interest: Author Dang, Vu Phuong Linh has received research grants from Hanoi School of Public Health and National Foundation for Science and Technology Development (Nafosted), Ministry of Science and Technology. Dr Dang acted as principal investigator of the study, developed the study design and analyzed data together with other members of research team. All authors were involved in doing research and writing of the manuscript and have approved the final version for this publication. We declare no conflict of interests.

Ethical approval: The ethical permission of the study has been approved by Hanoi University of Public Health, Hanoi, Vietnam.

References:

1. UNAIDS, UNAIDS report on the global AIDS epidemic. 2012.

2. HIV/AIDS, C.p.c., Tài liệu "HIV tại Việt Nam ước tính và dự báo giai đoạn 2011-2015.". 2013.

3. Goulder, P.J., et al., Paediatric HIV infection: correlates of protective immunity and global perspectives in prevention and management. Br Med Bull, 2001. 58: p. 89-108.

4. H V Pham, A.I., MD, L V Nguyen, C T T Phan, TT B Phung, K Takemoto, A N Pham, X Bi, MD, D. T. & Ichimura, K. K. and H, Two-year outcome of first-line antiretroviral therapy among HIV-1 vertically infected children in Hanoi, Vietnam. Int. J. STD AIDS, 2013.

5. Moore, R.D. and R.E. Chaisson, Natural history of opportunistic disease in an HIV-infected urban clinical cohort. Ann Intern Med, 1996. 124(7): p. 633-42.

6. Natural history of vertically acquired human immunodeficiency virus-1 infection. The European Collaborative Study. Pediatrics, 1994. 94(6 Pt 1): p. 815-9.

7. Nguyen Van Lam, P.N.A., Nghiên cứu căn nguyên, đặc điểm lâm sàng, cận lâm sàng viêm phổi do vi rút ở trẻ em nhiễm HIV tại bệnh viện Nhi Trung ương. Truyền nhiễm Việt Nam, 2015. số 2 (10), 68-72.

8. Nguyen Van Lam, P.N.A., Nghiên cứu viêm phổi do Pneumocystis Jiroveci trên bệnh nhi HIV/AIDS tại Bệnh viện Nhi Trung ương. Y học Việt Nam, 2013. 2, 108-112.

9. Nguyen Van Lam, P.N.A., Nguyen Thanh Liem, Ngo Thu Tuyen Căn nguyên gây viêm phổi trên trẻ nhiễm HIV điều trị nội trú tại Bệnh viện Nhi Trung ương năm 2010 - 2011. Nghiên cứu y học, 2012. 3A, 131-136.

10. WHO, WHO 2013 ART Guidline. 2013.

11. Concato, J. and A.R. Feinstein, Monte Carlo methods in clinical research: applications in multivariable analysis. J Investig Med, 1997. 45(6): p. 394-400.

12. Singh, S., et al., Clinical profile of 516 children affected by HIV in a tertiary care centre in northern India: 14 years of experience. Trans R Soc Trop Med Hyg, 2009. 103(6): p. 627-33.

13. Shah, I., Age related clinical manifestations of HIV infection in Indian children. J Trop Pediatr, 2005. 51(5): p. 300-3.

14. Fru, F.S., et al., Baseline demographic, clinical and immunological profiles of HIV-infected children at the Yaounde Gynaeco-Obstetric and Pediatric hospital, Cameroon. Pan Afr Med J, 2014. 17: p. 87.

15. Spira, R., et al., Natural history of human immunodeficiency virus type 1 infection in children: a five-year prospective study in Rwanda. Mother-to-Child HIV-1 Transmission Study Group. Pediatrics, 1999. 104(5): p. e56.

16. Stigma and discrimination fuel the HIV/AIDS epidemic. HIV Prev Plus, 2005. 6(2): p. 3.

17. Mahajan, A.P., et al., Stigma in the HIV/AIDS epidemic: a review of the literature and recommendations for the way forward. AIDS, 2008. 22 Suppl 2: p. S67-79.

18. Pursuing Later Treatment Options, I.I.p.t.f.t.C.o.O.H.I.V.E.R.E., et al., Risk of triple-class virological failure in children with HIV: a retrospective cohort study. Lancet, 2011. 377(9777): p. 1580-7.

19. Portela, M.C. and K.N. Simpson, Markers, cofactors and staging systems in the study of HIV disease progression: a review. Mem Inst Oswaldo Cruz, 1997. 92(4): p. 437-57.

20. Matin, N., et al., Clinical profile of HIV/AIDS-infected patients admitted to a new specialist unit in Dhaka, Bangladesh--a low-prevalence country for HIV. J Health Popul Nutr, 2011. 29(1): p. 14-9.

21. Yadav, J., S. Nanda, and D. Sharma, Opportunistic Infections and Complications in Human Immunodeficiency Virus-1-Infected Children: Correlation with immune status. Sultan Qaboos Univ Med J, 2014. 14(4): p. e513-21.

22. Jankowska, M., et al., [Opportunistic infections in HIV-positive patients hospitalized in the Clinic of Infectious Diseases AMG]. Przegl Epidemiol, 2001. 55 Suppl 3: p. 125-8.

23. Ghate, M.V., et al., Relationship between clinical conditions and CD4 counts in HIV-infected persons in Pune, Maharashtra, India. Natl Med J India, 2000. 13(4): p. 183-7.

24. Ghate, M., et al., Incidence of common opportunistic infections in HIV-infected individuals in Pune, India: analysis by stages of immunosuppression represented by CD4 counts. Int J Infect Dis, 2009. 13(1): p. e1-8.

25. Patton, L.L., et al., Oral lesions, HIV phenotypes, and management of HIV-related disease: Workshop 4A. Adv Dent Res, 2011. 23(1): p. 112-6.

26. Yazdanpanah, Y., et al., Incidence of primary opportunistic infections in two human immunodeficiency virus-infected French clinical cohorts. Int J Epidemiol, 2001. 30(4): p. 864-71.

27. Xiao, J., et al., Spectrums of opportunistic infections and malignancies in HIV-infected patients in tertiary care hospital, China. PLoS One, 2013. 8(10): p. e75915.