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International Journal of Nephrology and Urological Disorders

Research Article
ISSN 2577-0152

# Alterations of Clinical markers in HIV-Infected Children treated with Antiretroviral Therapy at the National hospital of Pediatrics, Vietnam

**Dang Vu Phuong Linh[1], Le Thi Kim Anh[1], Nguyen Thu Hoai[2], Pham Viet Hung[3], Nguyen Van Lam[3], Le Thanh Hai[3], Dang Minh Diem[1], Vu Thi Phuong[4]**

[1]*Hanoi University of Public Health, Hanoi, Vietnam*
[2]*National Geriatric Hospital, Hanoi, Vietnam*
[3]*National Hospital of Pediatrics, Hanoi, Vietnam*
[4]*Dinh Tien Hoang Institute of Medicine, Hanoi, Vietnam*

## Abstract

According to the guidance of the World Health Organization (WHO), children diagnosed with HIV infection should be treated with antiretroviral drugs (ARV) as soon as possible. After 36 period of following-up treatment, up to 21% of HIV infected patients were found to suffer from treatment failure, manifested by reduced CD4 T cell counts and increased HIV viral load. In addition, we also monitored other clinical markers during the course of treatment, therefore, we would like to investigate the alterations of these markers during the course of treatment to understand better the relationship between these clinical markers and the treatment response.The study was designed as nested case-control study, in which, 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. The study showed that the number of CD4 T cells, opportunistic infections and Alanine transaminase (ALT) levels during treatment are correlated with the ability to respond to treatment in HIV-infected children. In addition, the responders also recover better in terms of immunological and other biological markers including hemoglobin, platelets, and liver enzymes than non-responders. Therefore, monitoring these markers during the treatment can be beneficial in prognosis the treatment response.

**Keywords:** HIV, Clinical/subclinical markers, Treatment response, Antiretroviral therapy

**Corresponding author:** **Dang Vu Phuong Linh,**
IHanoi University of Public Health, Hanoi, Vietnam1A Duc Thang Road, North Tu Liem district, Hanoi, Vietnam.
**E mail:** dvpl@huph.edu.vn, phuonglinh.j@gmail.com

**Citation:** Dang Vu Phuong Linh et al. (2018), Alterations of Clinical markers in Hiv-Infected Children treated with Antiretroviral Therapy at the National hospital of Pediatrics, Vietnam. Int J Nep & Uro Dis. 2:2, 06-11.



**Received:** March 28, 2018
**Accepted:** April 8, 2018
**Published:** June 15 , 2018

## Introduction

In 2015, it is estimated 35 million people living with HIV and 10% of them are perinatal infected children [1]. In Vietnam, there are more than 215,000 people living with HIV, of which over 5,500 are children [2]. Overall, only 4% of the world's population infected with HIV whereas 20% of the AIDS death are children [3]. Numbers of research has shown the rapid progression of disease among HIV infected children 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 of ART initiation, up to 21% of the children suffered from treatment failure, manifested by a declined immune function and severely reduced general health [4]. Treatment failure often occurs as the consequence of drug resistance and immune-escape mutations of the HIV virus, especially in developing coultries, where the medical test to detect mutation is not implemented during the course of treatment, the patients would eventually 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 virus, leading to decreased levels of viral load to undetectable levels. Beside the ARV drugs, immune system is also considered to be one of the most effective modes to control viral infection. Therefore, with the condition of viral suppression when the treatment is initiated, 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, we observed that HIV infected children also suffered from high levels of treatment failure, coupled with increased viral load and decreased immune response.

Beside viral load and CD4 T cell counts, which are considered to be golden markers to monitor the treatment responses, other biochemical and hematological markers might play important roles such as liver enzyme Alanine transaminase (ALT) and Aspartate transaminase (AST), hemoglobin, platelet counts, triglycerides and opportunistic infections. The elevation of ALT and AST is usually found in certain diseases linked to liver abnormality including using epileptic drugs, anti-fungal and treated with ART. It is known that antiretroviral drugs including protease inhibitor might cause damage to liver cells, leading to increased levels of ALT and AST. However, such elevation is 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 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 as defined as the following: Cases (patients suffer from treatment failure or nonresponders): During follow-up of the treatment, patients has encountered one of these failures: clinical failure (the clinical stage of opportunistic infection in degree 3-4, according to WHO classification), immunological failure (the levels of CD4 T cells counts decreased more than 5% of that before treatment), or virological failure (HIV viral load more than 5,000 copies/ml) [10]. Controls are defined as patients without treatment failure occurred during 36 months of treatment. The patients, who had visited and received treatment at the National Hospital of Pediatrics from 2008 to 2012, were invited to participate in the study. After 36 month followed up, a total of 270 HIV infected children were 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:** 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 use 47 remaining controls.

**Analysis:** The characteristics of the HIV infected children between the two groups: responders and nonresponders were compared by Chi square test. Comparision between different levels of two groups were compared by non-parametric tests, with the significant level is less than 5%.

## Results

There were total of 54 cases and 47 controls included in the study. according to the table 1, the data showed no statistically significant difference between tf and ts groups in terms of sex, age and the levels of opportunistic infection at the to of the study.

Similarly, there was no statistically significant difference in CD4 T cell counts between TF and TS groups before treatment started (p=0.14) **(Figure 1)**. However, after the treatment started, TS group showed marked increased in CD4 T cell counts at higher rate than that of TF group. The difference between the two groups had reached statistically significant after 12 month of treatment. In addition, the increased levels of CD4 T cell counts in each groups also reached statistically significant difference during 36 month of treatment **(Figure 1)**.

The hemoglobin levels of both TS and TF groups raised during the course of treatment, even though the levels 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).

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

Table 2 presented the opportunistic infections (OIs) before and after 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 World Health Organization classification. On the contrary, on TF subjects, the prevalence of OIs was not significantly reduced before and after treatment initiated

| Characteristics | | TF | | TS | | p ($\chi^2$) |
|---|---|---|---|---|---|---|
| | | 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

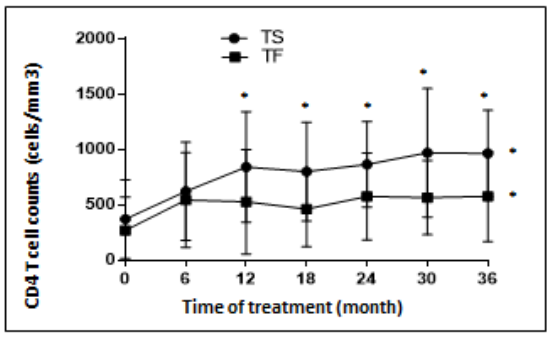
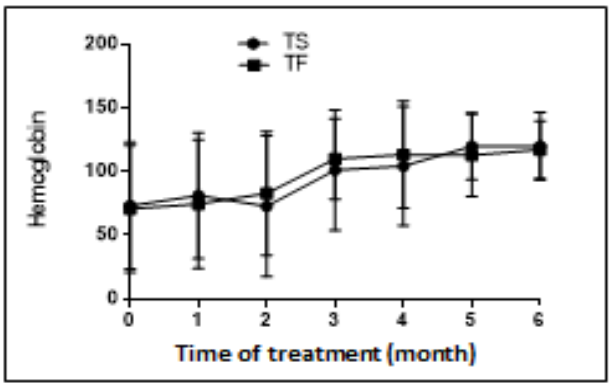



**Figure 1:** The changes in CD4 during the 36 months of treatment



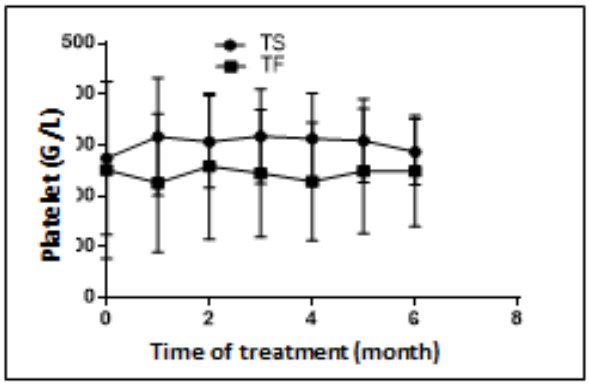
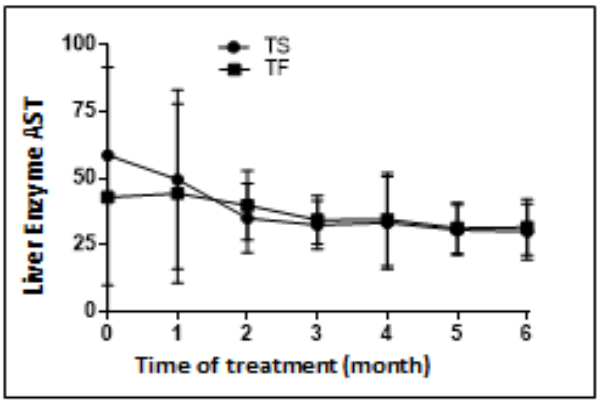




**Figure 2:** Hemoglobin and platelet levels during the treatment



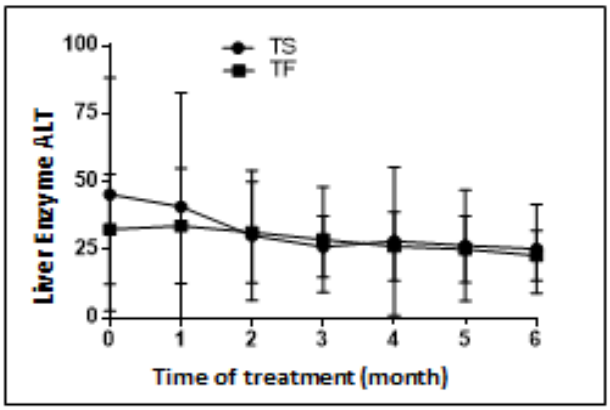




**Figure 3:** Liver enzyme ALT and AST levels during treatment

| Opportunistic infection | TS | | | | TF | | | |
|---|---|---|---|---|---|---|---|---|
| | Before treatment | | After treatment | | Before treatment | | After treatment | |
| Persistent generalized lymphadenopathy | 4 | 12,9 | 0 | 0 | 6 | 9,0 | 1 | 1,8 |
| Unexplained persistent Hepatospleno-megaly | 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

## Discussion

The results showed that among children diagnosed and treated for the first time, the children under one year of age accounted for less than 8% of the total, the 1-5 year old group accounted for highest proportion, followed by 5-10 years old group. The result is consistent with other studies conducted in developing countries such as Senegal, Rwada, India and Africa [11-14]. The delayed diagnosis was found to be correlated to low levels of education, social stigma and limited knowledge on HIV infection [15, 16]. Delayed diagnosis might be one of the causes of increased levels of treatment failure as these children showed certain levels of impaired immune system. In addition, these children were also fould to be infected with other opportunistic infections as well as to suffer from certain symptoms related to ART side-effect including anemia, impaired functions of different systems such as kidney, livers etc. HIV infected children in our study also showed such symptoms including anemia, impaired liver functions (manifested by elevated levels of liver enzyme), prolonged diarrhea and sleep disorders. TS group showed the greater ability to normalize the symptoms and eliminate the opportunistic infections during the 36 months of treatment compared to those of TF group.

The large-scale study called PLATO II and COHERE conducted in 1007 HIV infected children treated with ART showed that there were 5% of treatment failure after 5 years following up, which is much lower than that of developing countries and in our study [17]. 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 we did not 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 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 [13]. 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 [18]. 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). 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 in CD4 T cell counts and CD4 percentage at baseline between TS and TF groups. Similarly, there was no statistically significant difference in 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 [19]. Other studies have also shown that sex, number and percentage of CD4 cells at time To and clinical stage of OIs are not statistically correlated to treatment response in infants [19]. Based on the data, we might suggest that the recovery of the body and of the immune system might depend on factors other than CD4 T cell counts.

Prior to ART treatment, most patients included in the study had lower levels of CD4 T-cell counts, hemoglobin and higher levels of liver enzymes ALT, AST than those of normal children. There was no statistically significant difference between the two groups TS and TF

regarding the above factors. During the treatment, patients on both groups showed an improvement in terms of weight, height, CD4 T cell counts, hemoglobin, platelet levels, liver enzyme levels and HIV viral load. However, the improvement of the two groups was not uniformly similar, in TS group, the CD4 T cells counts increased up to 468 cells/mm3 whereas, TF group only reached 330 cell/mm3 after 36 month of treatment. Hemoglobin levels also increased in both groups especially in TS group. Similarly, the platelet levels were also increased although the levels have not reached the reference value. Regarding the liver enzyme, TS group managed to reduce AST and ALT to a reference value, whereas these levels were still high in TF group.

The number of CD4 T cell counts, opportunistic infections or hemoglobin levels might play roles on treatment response in HIV-infected children. Thus, the recovery of the immune system based on treatment might be important factor in the prognosis the treatment response. Opportunistic infections not only weaken the immune response but also complicate the immune system and thus treating opportunistic infections with antibiotics and other drugs might affect the ART response. Low hemoglobin, anemia was found to be associated with disease progression, and since ART was shown to lead to anemia in some patients, thus anemia caused by ART may be a mechanism closely related to the treatment response.

Our results showed that opportunistic infections in HIV-infected children was closely related to treatment failure, this may be explained by the fact that the treatment failure is usually associated with a decline in the immune system. Yadav J et al. also found a correlation between the severity and the prevalence of opportunistic infection with CD4 cell counts, in which the higher of the CD4 cells the lower severity and incidence of infectious diseases [20]. In the TS group, the prevalence of OIs decreased significantly, with only few children still acquired certain OIs of clinical stage 2 after treatment initiated. 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. The study also noted that up to 45% patients died from OIs including candidiasis, tuberculosis, pneumonia, and nervous system toxoplasmosis [21]. 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 [22, 23]. 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 [24]. 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 [20, 25, 26].

Overall, in TS groups, HIV infected children tend to recover better after the treatment initiated compared to TF group, thus monitoring the alterations of 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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