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ORIGINAL ARTICLE

# Clinical characteristics of pediatric HIV-1 patients treated with first-line antiretroviral therapy in Vietnam: a nested case–control study

**Minh Diem Dang[1] · Duc Minh Nguyen[2] · Huu Bich Tran[1] · Viet Hung Pham[3] · Daryl Spak[4] · Linh Chi Pham[5] · Thi Quynh Phan[1] · Thi Thanh Dinh[1] · Thi Kim Anh Le[1] · Van Lam Nguyen[2] · Thanh Hai Le[2] · Son Ngoc Hoang[6] · Vu Phuong Linh Dang[1]**

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**Abstract**
*Objectives* Over the past decades, Vietnam has made great strides in reducing the rate of mortality in HIV-related deaths, due to increased access of antiretroviral therapy (ART); however, given the significantly high level of treatment failure (TF), it is essential to identify markers that describe the failure of ART in HIV-1 infected children.
*Methods* A nested case–control study was conducted with clinical data collected from 101 HIV-infected children [26 TF and 75 treatment success (TS)] at National Hospital of Pediatrics, Vietnam (2008–2012).
*Results* The results showed that certain factors including height, weight, vaccination with Hepatitis B, and platelet were significantly different between TF and TS before starting the treatment. In addition, age to start the treatment, CD4 percentage, and opportunistic infection were found to significantly predict treatment outcome most frequently, implying the importance of clinical markers in the treatment response by Cox regression analysis.
*Conclusions* There is an inherent complexity within clinical markers that is challenging to determine HIV-pediatric failure and further research is needed to build a complete picture to guide clinical, evidence-based practice.

**Keywords** HIV-1 · Pediatric · Treatment failure · ART

## Introduction

In 2013, it was estimated that nearly 250,000 people living in Vietnam were infected with Human Immunodeficiency virus (HIV) (NCADP 2014). The increased use of antiretroviral therapy (ART) within the country has significantly reduced mortality/morbidity associated with infection by restoring immunologic functioning and reduced virus-related health outcomes. However, even with improvements being made with treatment effectiveness, the difficulty in successful treatment of HIV-infected children remains a major area of concern due to the persistence of HIV infection, reflected by significant levels of viral load despite of being treated with ART.

While the majority of HIV-infected patients living in Vietnam are men who have sex with men (MSM), intravenous-drug users, and adult women, children accounts for a portion of this population with 2% according to UNAIDS (NCADP 2014). Treatment of HIV-1 infected children in Vietnam is one of major issues for HIV management, the study of Pham et al. stated that despite ART initiation, many HIV-infected children treated with ART fail to respond to treatment, exhibiting a decline in immune function and severely reduced general health (Pham et al. 2013). ART failure is often a consequence of drug resistance and

M. D. Dang and D. M. Nguyen are first co-author.

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✉ Vu Phuong Linh Dang
dvpl@huph.edu.vn

1 Hanoi University of Public Health, Hanoi, Vietnam
2 National Hospital of Acupuncture, Hanoi, Vietnam
3 Vietnam National Hospital of Pediatrics, Hanoi, Vietnam
4 University of Buffalo School of Medicine and Biomedical Sciences, Buffalo, New York, USA
5 University of Washington, Seattle, Washington, USA
6 Viet Duc Hospital, Hanoi, Vietnam

mutations of the HIV virus, probably resulting in opportunistic infections and death if second-line ART is not initiated.

Due to the high rate of ART treatment failure within infected children, identification of infection progression is of particular importance within this population. Previous research has found the rate of TF to be significantly higher in children when compared to their infected adult counterparts being treated with similar therapies (Mullen et al. 2002). Number of researches have identified a number of markers associated with disease progression and treatment response, including characteristics of HIV-infected patients, incomplete adherence, virologic failure, drug resistance, subtypes of virus, and immunological markers including CCR5/CXCR4 chimeric receptor, and levels of CD38 expression on T cells (Cavarelli et al. 2008; Resino et al. 2004; Sebunya et al. 2013; Teshome et al. 2014). The cross-sectional study in Tanzania by Emmett et al. concluded that clinical and immunologic standards were insufficient for identifying children with HIV-1 failure. Emmett et al. made the claim for a low-cost HIV-RNA device that would be effective in monitoring HIV-1 treatment (Emmett et al. 2010). We propose that the appearance of viral load could be a consequence of treatment failure coupled with the failure of immune system combating against HIV virus. Furthermore, high levels of viral load are often linked to the reduction of certain clinical markers including immunological, biochemical, and hematological markers. In our clinical setting, we have monitored the clinical markers in 101 HIV-1-infected children enrolled at National Hospital of Pediatrics, Hanoi, Vietnam, who were strictly adhered to the ART treatment from 2008 to 2012 and we found significant proportion of treatment failure. Therefore, we would like to identify markers that would describe the failure of ART in HIV-1 infected children to guide clinical management for these patients in the present and long-term.

## Methods

With the aim of identifying the markers that would facilitate the prediction of TF, we conducted the nested case–control study (retrospective study), in which, the study subjects were chosen from the outpatients being recruited in our previous prospective study conducted in National Hospital of Pediatrics (NHP), Hanoi, Vietnam, from 2008 to 2012 (Hung et al. 2014). We monitored all HIV-infected children that underwent treatment in NHP for the first time with first-line ART, which contains one non-nucleoside reverse transcriptase inhibitor (Nevirapine) and two nucleoside reverse transcriptase inhibitors (Stavudine or Zidovudine and Lamivudine) in 2008 and followed up until 2012. Of the total recruited patients, during the following up time, only 300 patients were found to be strictly adherent to ART treatment. All the blood samples of HIV-infected patients were used to analyze biochemical, hematological, and immunological analysis for every 6 months during 36 months of following up time. The data were collected in medical record for each patients.Of total 300 patients, only 101 patients had enough information regarding the clinical markers collected every 6 month, in the medical records within 36 month of following up.

Cases were identified as patients who did not respond to ART following 36 months from the point of beginning treatment and classified as treatment failure (TF). In accordance with WHO guidelines, treatment failure occurs when: viral load is >5000 copies/mL (WHO 2010). In contrast, controls were identified as patients who did respond to treatment and did not meet the criteria for treatment failure; these patients were classified as treatment success (TS). The independent variables collected at the beginning of the treatment include: age, gender, ART prophylaxis for the prevention of mother–to-child transmission of HIV, antiretroviral (ARV) prophylaxis for the newborn, and HBV vaccination; and those collected every 6 month include: height, weight, opportunistic infection (1–4 clinical stage according to WHO guidelines), serum hemoglobin, platelet count, CD4 T cell count, CD4 percentage, CD8 T cell count, CD3 T cell count, HIV RNA viral load, liver enzyme serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), Creatinine, Cholesterol, Triglyceride, Lymphocyte percentage, Numbers of Red blood cell and White blood cell, Neutrophil percentage, Platelet, Hemoglobin, Hematocrit, Mean corpuscular hemoglobin (MCH), Mean corpuscular volume (MCV), and Corpuscular hemoglobin concentration (MCHC). The data were collected and managed by Epidata 3.1 and analyzed by Stata 12.0.20 for descriptive statistic, statistical inference, and survival analysis. The descriptive statistic was used to summarize the variables at time 0 of TF and TS groups, whereas the statistical inference was used to compare different variables at T0 of the two TF and TS groups. The Cox analysis, on the other hand, was used to analyze the relation between different variables and the appearance of the treatment failure.

## Results

### Characteristics of treatment failure and treatment success

The health records and blood sample data from a total of 101 HIV-infected child patients at National Pediatrics Hospital were included within statistical analysis. Of the total 26 and 75 subjects in TF and TS group, respectively, 17

(73.1%) and 49 (65.3%) were males. There were significant differences in the status of HBV vaccination, weight, and height between TF and TS groups at time 0 (T0 defined as the baseline levels before patients started the ART treatment). However, we did not observe any significant difference in the age to start the treatment and the status of opportunistic infection (Table 1).

Except for the levels of platelet, the median levels of that of TF is 219 (14–588) compared to that of TS is 281 (5–650) ($p=0.029$), other factors did not show any significant difference between TF and TS groups at T0, even though the levels of CD4 T cell count were higher in TS compared to that of TF [212.5 (27–1738) and 273.5 (18–1225), respectively]. On the contrary, we also found higher levels of CD8 T cell count and CD3 T cell count in TF compared to those in TS and reduced levels of other markers such as SGOT, SGPT, Creatinine, Cholesterol, Triglyceride, and Red blood cell levels in TF compared to those in TS, even though the data are not statistically significant (Tables 2, 3).

### Clinical predictors of ART treatment failure

We analyzed the correlation between clinical markers (independent variables) and appearance of the treatment failure using Cox regression model (uni-variable) through 36 month of treatment (with 6 time points) and showed that age to start the treatment, CD4T cell count, CD4T percentage, status of opportunistic infection, HBV vaccination, Weight, Platelet, and levels of liver enzyme SGPT were significantly correlated with treatment response (Table 4).

However, when using multi-variable Cox regression model, only certain variables including age to start the treatment, CD4 T cell counts and CD4 percentage, and status of opportunistic infection were correlated with the treatment response, in which, the higher age to start the treatment might have 1.5 time higher rate to develop treatment failure, and the appearance of opportunistic infection and the WHO degrees of opportunistic infection showed the significant correlation with the treatment failure.

## Discussion

The results noted greater proportion of male compared to female patients, the high incidence and severity of HIV infection in male children have also been previously investigated in a number of research (Fru et al. 2014; Lodha et al. 2006; Mori et al. 2015; Shah 2005). Other studies have also reported that female patients tend to respond better to ART treatment than male counterparts (Shiau et al. 2014; Takarinda et al. 2015). We also observed two male patients that died at the end of the study; however, the data were too limited to perform statistical analysis. A further study is needed to understand the biological mechanisms and clinical significance of the sex difference.

The majority of HIV children were diagnosed at late stage (median age to start the treatment in TF and TS groups were 4.6 and 4.1, respectively), when the immune system was already distorted and thusly greatly affecting the treatment response. Delayed diagnosis and treatment might explain the significant high rate of treatment failure in Vietnam. The results are consistent with finding conducted in developing countries in which the average age for HIV diagnosis was 60 months of age in Senegal, 56 months Rwanda, and 54 months in India. In contrast, the

**Table 1** Characteristics of Treatment failure and Treatment success groups at T0 (data taken from National Hospital of Pediatrics, Hanoi, Vietnam 2008–2012)

| Factors | Sex | | | | HBV vaccination | | Opportunistic infection | |
|---|---|---|---|---|---|---|---|---|
| | TF | | TS | | TF | TS | TF | TS |
| | Male | Female | Male | Female | | | | |
| *N* | 17 | 9 | 49 | 26 | 6 | 44 | 10 | 25 |
| % | 73.1 | 26.9 | 65.3 | 34.7 | 23.1 | 58.7 | 40 | 34.7 |
| $p$ ($\chi^2$) | 0.32 | | | | **0.002** | | 0.41 | |

| Factors | Age to start ART treatment | | Weight | | Height | |
|---|---|---|---|---|---|---|
| | TF | TS | TF | TS | TF | TS |
| Median | 4.6 | 4.1 | 15.5 | 13 | 108 | 95 |
| Min | 1.3 | 1.3 | 7.5 | 5.5 | 83 | 76 |
| Max | 10.9 | 12.6 | 27 | 41 | 127 | 140 |
| $p$ (Mann–Whitney) | 0.113 | | **0.04** | | **0.002** | |

*TS* Treatment success; *TF* treatment failure

**Table 2** Clinical characteristic of treatment failure and treatment success groups at T0 (data taken from National Hospital of Pediatrics, Hanoi, Vietnam 2008–2012)

| Clinical factors | Median | Min | Max | *P* (Mann–Whitney) |
|---|---|---|---|---|
| CD4 T cell count | | | | |
| TF | 212.5 | 27 | 1738 | 0.56 |
| TS | 273.5 | 18 | 1225 | |
| CD4 percentage | | | | |
| TF | 17.4 | 22 | 31.5 | 0.16 |
| TS | 11 | 0.7 | 29 | |
| CD8 T cell count | | | | |
| TF | 1334 | 1247 | 1421 | 0.22 |
| TS | 708 | 406 | 1680 | |
| CD3 T cell count | | | | |
| TF | 1856 | 1769 | 1943 | 0.2 |
| TS | 935 | 80 | 1834 | |
| Liver enzyme serum glutamic oxaloacetic transaminase—SGOT (U/L) | | | | |
| TF | 39 | 26.2 | 142.4 | 0.68 |
| TS | 42.9 | 16 | 361 | |
| Liver enzyme serum glutamic pyruvic transaminase—SGPT (U/L) | | | | |
| TF | 24.7 | 14.8 | 129.7 | 0.36 |
| TS | 27.4 | 10.1 | 231.6 | |
| Creatinine (μmol/L) | | | | |
| TF | 44.1 | 44.1 | 48.1 | 0.78 |
| TS | 63.5 | 36 | 92 | |
| Cholesterol (mmol/L) | | | | |
| TF | 3.4 | 2,6 | 4.9 | 0.43 |
| TS | 3.8 | 2.7 | 5.2 | |
| Triglyceride (mmol/L) | | | | |
| TF | 1.2 | 0.2 | 1.7 | 0.66 |
| TS | 1.3 | 0.6 | 4.2 | |
| Lymphocyte percentage | | | | |
| TF | 34.6 | 17.8 | 78.1 | 0.38 |
| TS | 43.3 | 2.4 | 68.7 | |
| Red blood cell (T/L) | | | | |
| TF | 3.9 | 3.1 | 5.4 | 0.28 |
| TS | 4.2 | 3.2 | 8.4 | |
| White blood cells (G/L) | | | | |
| TF | 8.4 | 2.6 | 13.9 | 0.87 |
| TS | 8.1 | 4.8 | 16.2 | |
| Neutrophil percentage | | | | |
| TF | 52.95 | 14.3 | 67.2 | 0.063 |
| TS | 35.3 | 3.8 | 84.8 | |
| Platelet (G/L) | | | | |
| TF | 219 | 14 | 588 | **0.029** |
| TS | 281 | 5 | 650 | |
| Hemoglobin (g/L) | | | | |
| TF | 107.5 | 10.7 | 144 | 0.867 |
| TS | 109 | 9.2 | 155 | |
| Hematocrit (%) | | | | |
| TF | 33.7 | 22.4 | 40.5 | 0.828 |
| TS | 33.45 | 3.2 | 42.5 | |
| Mean corpuscular hemoglobin—MCH (pg) | | | | |

**Table 2** (continued)

| Clinical factors | Median | Min | Max | *P* (Mann–Whitney) |
|---|---|---|---|---|
| TF | 26.1 | 15.2 | 35.4 | 0.866 |
| TS | 26.8 | 8.7 | 83.8 | |
| Mean corpuscular volume—MCV (fL) | | | | |
| TF | 83.9 | 51 | 104 | 0.766 |
| TS | 79.95 | 53.8 | 324 | |
| Corpuscular hemoglobin concentration (MCHC) (g/L) | | | | |
| TF | 326 | 298 | 359 | 0.685 |
| TS | 325 | 28.5 | 356 | |

*TS* Treatment success; *TF* treatment failure

**Table 3** The correlation between factors including age to start the treatment, clinical markers (CD4 T cell count, CD4 percentage and SGPT), and opportunistic infection (dependent variables) with the treatment response (dependent variables: TF/TS) analyzed by Cox regression analysis through 36 months of treatment (data taken from National Hospital of Pediatrics, Hanoi, Vietnam 2008–2012)

| Prognosis factors | HR* | 95% CI | |
|---|---|---|---|
| Age to start treatment | 1.12 | 1.06 | 1.19 |
| CD4 T cell count | 0.999 | 0.998 | 0.999 |
| CD4 percentage | 0.95 | 0.92 | 0.97 |
| Opportunistic infection | 0.69 | 0.499 | 0.95 |
| HBV vaccination | 0.29 | 0.19 | 0.44 |
| Weight | 0.96 | 0.93 | 0.99 |
| Platelet | 0.998 | 0.996 | 0.999 |
| Drug resistant mutation | 1.72 | 1.23 | 2.4 |
| SGPT | 0.98 | 0.96 | 1 |

The prognosis factors collected during the time of the study were used to run the univariable Cox regression analysis with the appearance of the treatment failure, only those significantly correlated to the treatment response were chosen to present on the Table 3

*Hazard Ratio was analyzed by univariable Cox regression analysis

**Table 4** The correlation between factors and the treatment response (dependent variables: TF/TS) analyzed by Cox regression analysis through 36 months of treatment

| Prognosis factors | HR* | 95% CI | |
|---|---|---|---|
| Age to start treatment | 1.49 | 1.3 | 1.69 |
| CD4 T cell count | 1.00 | 1.00 | 1.002 |
| CD4 percentage | 0.96 | 0.927 | 0.994 |
| Opportunistic infection | 0.69 | 0.40 | 1.19 |
| WHO degree of opportunistic infection | 0.901 | 0.639 | 1.27 |
| HBV vaccination | 0.3 | 0.18 | 0.51 |

The prognosis factors that were significantly correlated to the treatment response analyzed by uni-variable Cox regression were chosen to analyze by multi-variable Cox regression

*Hazard Ratio was analyzed by multi-variable Cox regression analysis

age in certain regions of Africa and developed countries is much lower (Fru et al. 2014; Shah 2005; Singha et al. 2009; Spira et al. 1999). Numerous researchers showed that the introduction of combination ART during the first year of life preserves immune function and suppresses the HIV viral load to undetectable levels (Koller et al. 2015; Prato et al. 2015). In line with these findings, we also observed the age difference in TS and TF and that the age to start the ART treatment is one of the crucial factors to determine the treatment response.

Delayed treatment could be the consequence of the lack of communication between hospitals or technical support for HIV diagnosis in peripheral/remote medical centers. All HIV-infected mothers hospitalized in Hanoi Obstetrics Hospital were treated with ART during their pregnancy and the children were diagnosed with HIV as soon as they were born (Cao et al. 2014). However, most of the patients were born in rural hospitals, where HIV diagnosis is not applicable. Delayed diagnosis may result in difficulty in treatment when the immune system is compromised by infectious opportunistic diseases and reduced functions of several body systems including liver, kidney, and elevated side effects of ART drug. The side effects include anemia, liver poisoning (indicated by liver enzyme levels), persistent diarrhea, sleeping disorder, etc. Treatment for opportunistic infections is another complex issue. With TF children, their compromised immune system lead to increased opportunistic infections coupled with their reduced functions of body systems as reflected by abnormal levels of liver enzymes and hemoglobin. On the contrary, TS group showed the increased ability to eliminate of opportunistic infection upon the treatment started.

Additionally, our findings noted the significant difference between height and weight of TS and TF, the difference might have reflected the fact that the average age of TF is higher than that of TS (data not shown). Even though the immune system has been shown to strongly associate with nutrition, the damage of immune system reflected by

levels of CD4 T cell counts was not significantly different between the two groups. In addition, malnutrition and developmental delay including neurocognitive disorders were found to have higher prevalence in HIV-infected children and that nutrition has shown to have positive effect on the survival of HIV-infected children after initiation of antiretroviral treatment (ART) (Bineyam et al. 2010; Pedrini et al. 2015).

The platelet levels in TF were found to be significantly higher in TF compared to that of TS. The results were consistent with numbers of finding in which the levels of platelet were elevated in HIV-infected children (Kibaru et al. 2015; Kumar et al. 2012). However, we did not find any significant correlation between the platelet levels and treatment response.

Most children in the study had opportunistic infections at T0. This is consistent with study conducted by Fru et al., in which the number of children infected with HIV-related opportunistic infections was 83.5%, including tuberculosis, Human Hepatitis B and C, Cryptococcal infection, malaria, etc (Fru et al. 2014). According WHO guidelines for HIV clinical stages 1–4, most children with HIV were diagnosed with clinical stage 2–3 at the time of diagnosis. Only TS group could eliminate the infection after 36 months of treatment and at T5, the clinical stage was reduced to stage 1; however the clinical stage of opportunistic infection in TF remained the same. The finding suggested that the improvement of CD4T cells as well as the improvement of physical status could be linked to the ability to combat opportunistic infection. Further studies should attempt to assess duration of opportunistic infection as opposed to presence of absence for a better indication of treatment success/failure. In addition, patients with HBV vaccination tend to response better to the treatment; this might due to the fact that reducing other opportunistic infection might have resulted in better immune response against HIV. The opportunistic infection was found to be strongly associated with the treatment response; however our results with opportunistic infection seem to show that opportunistic infection might have the protective effect against the treatment failure, this might due to the fact that all patients have opportunistic infection and were treated with opportunistic infection before starting the ART treatment, thus patients were successfully treated with opportunistic infection might have higher chance of treatment response.

CD4T cell count has been reported to be an important indicator to monitor the progression of HIV-1 (Hung et al. 2014; Matin et al. 2011). This finding is supported by other studies that reported the association between treatment failure and lower CD4T cell count (Teshome et al. 2014). At T0, most of the research subjects showed significantly lower CD4T cell count, hemoglobin levels, and higher levels of liver enzymes SGOT and SGPT than those of healthy children. During the course of treatment, HIV-infected children in both groups TS and TF showed significant improvements including weight and height, increased CD4 counts, hemoglobin and platelet levels, reduced levels of SGOT and SGPT as well as reduced HIV viral load. However, the degree of improvement was much more profound in TS compared to that of TF and some of TS could normalize these factors to almost normal levels in healthy donors. CD4 percentage was strongly correlated to the treatment response, implying the importance of the immune system in combating the HIV virus.

Our results suggest that the recovery of immune system reflected by CD4T cell count, the status of the opportunistic infection as well as the age to start the treatment could be some of the most important prognosis factors for treatment response. Starting treatment at early age, when the immune system was still intact, was the most important for HIV treatment management.

The study has numbers of limitations. First of all, the study is the retrospective study and the data were collected in the medical record of patients, thus there were some patients with missing clinical data especially in the treatment success group. Second, we collected data only in National Hospital of Pediatrics, so that the data were limited and this might affect numbers of the analysis.

In conclusion, data showed that certain clinical factors could imply the treatment response; however, further study is needed to build a complete picture to guide clinical, evidence-based practice.

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**Compliance with ethical standards**

**Conflict of interest** 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 National Hospital of Pediatrics, Hanoi, Vietnam.

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