

# Elevation of immunoglobulin levels is associated with treatment failure in HIV-infected children in Vietnam

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**Background:** HIV-infected children suffer from higher levels of treatment failure compared to adults. Immunoactivation, including humoral immunoactivation reflected by increased immunoglobulin levels, is believed to occur early during HIV infection. Therefore, we wanted investigate alteration in immunoglobulin levels in association with treatment response in HIV-infected children.

**Methods:** A nested case-control study was conducted using clinical data collected from 68 HIV-infected children enrolled at the National Hospital of Pediatrics, Vietnam.

**Results:** The results showed that immunoglobulin levels, CD4 T-cell counts, CD4 T-cell percentage, and HIV load were significantly higher in the treatment-failure group than the treatment-success group at treatment initiation. IgG and IgA levels were negatively correlated with CD4 T-cell counts ( $P=0.049$  and  $P<0.01$ , respectively) and positively correlated with HIV load ( $P=0.04$  and  $P=0.02$ , respectively). In addition, IgG and IgA levels were independently associated with treatment response, analyzed by Cox regression analysis (HR 1.19 [ $P=0.049$ ] and HR 1.69 [ $P<0.01$ ], respectively).

**Conclusion:** Elevation of IgA levels occurred early during HIV infection, and might have a prognostic role in treatment response.

**Keywords:** antiretroviral therapy, HIV1, immunoglobulin, IgG, IgA, treatment failure

## Background

In 2016, there were ~2.1 million children infected with HIV worldwide and about 6,500 children infected with HIV in Vietnam.<sup>1,2</sup> The course of HIV infection in children is far from completely understood, since the immunoresponse against HIV of children is different from adults. Early diagnosis followed by antiretroviral therapy (ART) initiation has been shown to reduce HIV-related mortality and long-term morbidity successfully. However, children with ART still suffer from certain problems, including drug toxicity and development of drug resistance, partly as the consequence of incomplete immune-system recovery.

Children infected with HIV exhibit a generalized immunoactivation. T-cell activation is reflected in upregulation of CD38, HLA-DR, and Ki67 coexpression on CD4 and CD8 T cells.<sup>3-7</sup> B-cell activation, characterized by increased levels of immunoglobulin including hypergammaglobulinemia, elevation of IgA levels, increased susceptibility to B-cell lymphomas, spontaneous in vitro production of immunoglobulin by peripheral blood mononuclear cells, overexpression of activation markers, increased expression of apoptotic/exhaustion markers, and increased susceptibility to apoptosis and terminal differentiation of B cells, has been shown to occur during HIV infection.<sup>8-12</sup> Other B-cell populations, including activated mature B cells, plasmablasts,

immature/transitional B cells, and tissue-like memory B cells, have also been reported to increase during HIV infection.<sup>6,13–17</sup> Hypergammaglobulinemia is considered one of the most common hallmarks of HIV infection. de Milito showed that levels of hypergammaglobulinemia were associated with levels of B-cell activation, and thus hypergammaglobulinemia might reflect levels of generalized B-cell activation.<sup>10</sup> Research conducted to investigate mechanisms underlying hypergammaglobulinemia has shown that the elevation of IgG could be the consequence of increased B-cell activation/differentiation, polyclonal B-cell activation, and activated naïve B cells. As these B-cell subpopulations have been shown to be elevated as the consequence of viral replication and since these cells are not properly differentiated, they might produce low-specificity antibodies.<sup>10,15</sup> Titanji et al showed an inverse correlation between hypergammaglobulinemia and CD4 T-cell counts, suggesting that hypergammaglobulinemia occurs in concert with poor immunoresponse.<sup>11,12</sup> Hypergammaglobulinemia has also been found in viremic patients, while aviremic patients suffer from only slightly increased IgG levels.<sup>15</sup> Even though ART can suppress HIV replication and reduce the HIV-related effects,<sup>18</sup> the immune system has been shown to normalize only partially. ART can restore a large proportion of resting naïve B cells; however, antigen-specific antibody levels and memory B cells do not spontaneously recover. Similarly, immunoglobulin levels do not normalize completely, implying the irreversible destruction of B-cell compartments.

Increased IgA levels are also reported in HIV-infected children, and seropositive children suffer from higher levels of all immunoglobulins compared to seronegative children.<sup>19,20</sup> The association between IgA levels and CD4 T-cell counts, as well as HIV load, has not been completely proven, and IgA levels decrease as a consequence of ART treatment.<sup>21–24</sup>

In adults, the dysregulation of B cells by HIV has been studied extensively, whereas in children this has not been well characterized. In HIV vertically infected children, even though ART can reduce substantial levels of HIV viremia, the percentage of treatment failure in children is much higher than in their adult counterparts. We suppose that the immune system of HIV-infected children might behave differently compared to their adult counterparts; therefore, we would like to investigate alterations in immunoglobulin levels of HIV-infected children in relation to treatment response, in order to answer the question of whether immunoactivation can serve as a prognostic marker for treatment response.

## Methods

### Subjects

This was a nested case–control study, the data for which were drawn from a study on ART treatment in HIV-infected children at the National Hospital of Pediatrics (2008–2012).<sup>25</sup> These children had been treated and monitored with HIV medication, clinical examination, and counseling conducted periodically. Samples were collected every 6 months and plasma isolated and stored at  $-80^{\circ}\text{C}$  for further analysis. After 36 months' follow up, there were only 33 patients with full information in the treatment failure (TF) group, and thus we randomly chose 35 patients from the treatment success (TS) group.

Cases were identified as patients who had not responded to ART in 36 months from the point of beginning treatment and classified as TF. In accordance with WHO guidelines, TF occurs when viral load is  $>5,000$  copies/mL.<sup>26</sup> In contrast, controls were identified as patients who did respond to treatment and did not meet the criteria for TF. These patients were classified as TS.

### Sample collection

Data were collected from the medical record of each patient. Blood was collected in EDTA tubes, centrifuged to collect serum, and stored at  $-80^{\circ}\text{C}$  for further analysis. IgG, IgA and IgM were measured by automatic immunoassay according to the manufacturer's instructions. Briefly, serum was incubated with antibodies linked with biotin (antibodies specific for IgG, IgA, or IgM), then with streptavidin-coated microparticles. In this stage, samples are bound to the solid phase by reaction between biotin and streptavidin. Each sample was then aspirated into a measuring cell, where the microparticles were captured onto the surface of the electrode and unbound substances removed. Voltage was applied to the electrode, which then induced chemiluminescent emission, and the emission was captured by a photomultiplier.

### Data management and analysis

Data were entered into Excel and analyzed using Stata. Nonparametric, two-sided Wilcoxon–Mann–Whitney and  $\chi^2$  tests were used for comparison between different subject groups. Associations between immunoglobulin levels and clinical parameters were determined using Spearman's rank correlation for univariate and multivariate regression, with  $P < 0.05$  considered significant. The prognostic role of immunoglobulin levels in the development of TF were analyzed by Cox regression (univariate and multivariate regression).

Ethical permission for this study was granted by Hanoi University of Public Health, Hanoi, Vietnam.

## Ethics statement

Ethical permission for this study was granted by the Hanoi University of Public Health, Hanoi, Vietnam. Parental consent was not required by the university's ethical committee, since this research was conducted as a nested case-control study and samples and data had already been collected in longitudinal study, in which the parents of patients had the study explained to them and were asked to sign parental consent. We declare that all patient information was confidential and compliant with the Declaration of Helsinki.

## Results

There were 68 HIV-infected children enrolled in the study (Table 1). In the TS group, 57.1% were female, whereas this figure was only 12.1% female in the TF group. Female numbers in the TF group were significantly lower than the TS group ( $P=0.05$ ). Patients in the TF group had significantly lower CD4 T-cell counts and CD4 percentages than TS subjects (103.5 vs 258, respectively;  $P<0.001$ ). In addition, HIV RNA levels were higher in the TF group than the TS group at treatment initiation (145,000 vs 86,000, respectively;  $P<0.01$ ).

Serum levels of IgA were significantly higher in TF than TS subjects at treatment initiation (1.96 g/L vs 1.02 g/L, respectively;  $P<0.01$ ); however, after treatment initiation, we did not observe any significant decrease in IgA levels in either group (Figure 1). Serum levels of IgG, on the other hand, were not significantly different between the groups at treatment initiation; however, after treatment initiation, we found that only the TS group had significantly reduced IgG levels (13 g/L vs 11.1 g/L, respectively;  $P=0.04$ ).

Using univariate regression analysis, we found that serum IgA levels were negatively correlated with CD4 T-cell counts and ART timing in all HIV-infected children ( $R=-0.34$  [ $P<0.01$ ] and  $R=-0.209$  [ $P=0.04$ ], respectively; Table 2). On the contrary, IgA levels were found to be positively correlated with HIV load and age at starting treatment ( $R=0.38$  [ $P<0.01$ ] and  $R=0.47$  [ $P<0.01$ ], respectively). IgA concentrations were also found to be positively correlated with IgG and IgM levels (data not shown), suggesting that hypergammaglobulinemia might coincide with other humoral immunoresponses, including IgA and IgM. IgG levels were negatively correlated with CD4 T-cell counts ( $R=-0.46$ ,  $P=0.049$ ) and positively correlated with HIV viral load ( $R=0.35$ ,  $P=0.04$ ).

However, using multivariate analysis, we found that IgA levels were correlated only with age at treatment start and CD4 T-cell counts ( $R=-0.001$  [ $P=0.02$ ] and  $R=0.2$  [ $P<0.01$ ], respectively), whereas IgG levels were associated only with CD4 T-cell counts ( $R=-0.012$ ,  $P=0.021$ ). We analyzed correlations between IgG, IgA, and IgM levels (independent variables) and the appearance of TF using Cox regression (univariate and multivariate) through 36 months of treatment, and found that both IgG and IgA levels were significantly correlated with treatment response (HR 1.19 [ $P=0.049$ ] and HR 1.49 [ $P=0.03$ ], respectively; Table 3), whereby patients with higher IgA levels were 1.5 times more likely to develop TF than patients with low IgA levels. Similarly, patients with higher IgG levels were 1.2 times more likely of developing TF than patients with lower IgG levels. However, using multivariate analysis, we observed a significant association only of IgA levels with TF.

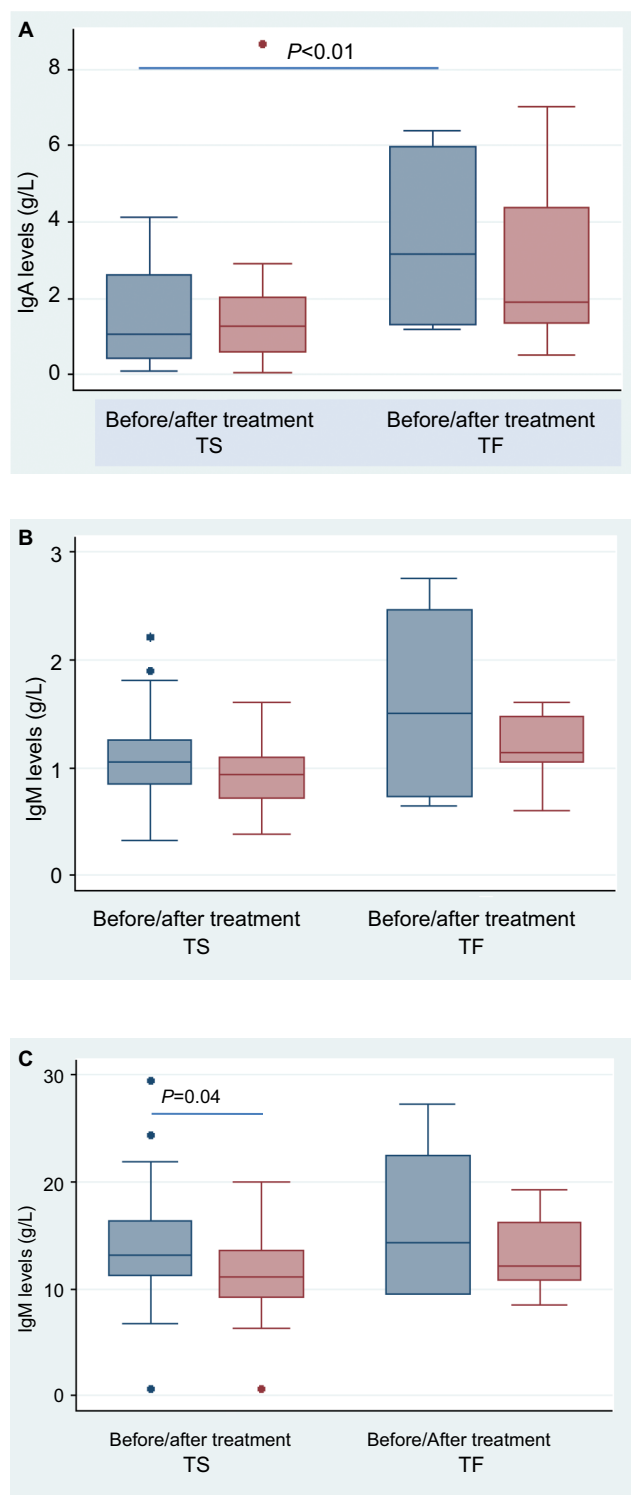
## Discussion

In this study, we found that immunoglobulin levels, CD4 T-cell counts, CD4 T-cell percentages, and HIV load were

**Table 1** Characteristics of TF and TS groups

Factors	Age at ART start		CD4 T-cell counts		CD4 T-cell percentage		HIV RNA	
	TS	TF	TS	TF	TS	TF	TS	TF
Median	4.2	4.7	258	103.5	8.7	7	86,000	145,000
Minimum	1.3	1.3	6	28	2.1	1.9	400	25,000
Maximum	9	12.6	1,177	1,186	38.8	27.9	600,000	13,000,000
P (Mann–Whitney)	0.11		<0.001		<0.001		<0.001	
Factors	Sex				Opportunistic infection			
	TS		TF		TS	TF		
	Male	Female	Male	Female				
n	15	20	29	4	40	18		
%	42.9%	57.1%	87.9%	12.1%	69%	31%		
P ( $\chi^2$ )	0.05				0.26			

**Abbreviations:** ART, antiretroviral therapy; TF treatment failure; TS, treatment success.



**Figure 1** IgG, IgM, and IgA levels before and after treatment initiation.

**Notes:** (A) IgA levels were significantly higher in the TF group than the TS group at treatment initiation. (B) The TS group had IgG levels successfully suppressed, while patients in the TF group showed no significant reduction between pre- and posttreatment. (C) There were no significant differences in IgM levels between the TF and TS groups or between each group before and after treatment initiation.

**Abbreviations:** TF, treatment failure; TS, treatment success.

significantly higher in the TF group than the TS group at treatment initiation. IgG and IgA levels were negatively correlated with CD4 T-cell count and positively correlated with HIV load. In addition, IgG and IgA levels were independently associated with treatment response on Cox regression analysis, and elevated IgA levels were associated with TF analyzed by multivariate regression analysis.

CD4 T-cell counts, CD4 T-cell percentages, and HIV load were significantly higher in TS than TF subjects in this study. The measurement of both percentages and absolute numbers of circulating CD4 T cells remains one of the most important parameters for monitoring treatment response in both adults and children.<sup>27,28</sup> Lewis et al found a recovery in the CD4 T-cell pool, especially naïve T cells, after initiation of ART, and this recovery was associated with the duration of infection.<sup>29</sup> We found that depletion of CD4 T cells occurred prior to treatment initiation and that levels of depletion might be associated with treatment response. HIV RNA is also considered a good marker to predict treatment response, and researchers have claimed that HIV RNA is a better marker than CD4 T-cell count in prognosis of treatment response.<sup>25</sup> We also observed higher viral replication in the TF group than the TS group at treatment initiation. Poor immunological function coupled with high levels of viral replication were significantly associated with TF.

Median IgA levels in the TF group were also found to be higher than those in the TS group at baseline, suggesting that immunoactivation might occur early during the course of HIV infection if there were an association between lower immunoactivation and TS. However, after treatment, only IgG levels were significantly reduced in both groups, suggesting difficulties in normalizing mucosal immunity. Mucosal immunoresponse has been shown to be significantly distorted at early stages of HIV infection, as characterized by early depletion of mucosal CD4 T cells.<sup>30,31</sup> The results indicated that monitoring immunoactivation prior to treatment initiation might be beneficial in prognosis of treatment response.

The increase in IgG levels found in HIV-infected children is consistent with other findings, implying elevation of polyclonal B-cell activation is associated with advancing disease.<sup>10</sup> Consistently with our findings, Lyamyua et al found that HIV-seropositive children tended to have higher levels of immunoglobulin than their seronegative counterparts.<sup>19</sup> However, our results showed no significant difference in IgM levels between the TS and TF groups or between each group prior to and after treatment initiation. Carrillo et al investigated the discordant regulation between IgM B cells

**Table 2** The association between clinical characteristics and immunoglobulin levels in HIV infected children analyzed by univariate and multivariate regression analysis

Factors	IgA		IgM		IgG			
	R	P-value	R	P-value	R	P-value		
CD4 T-cell count	−0.34	<0.01	0.02	0.85	−0.46	0.049		
CD4 T-cell percentage	−0.20	0.17	−0.04	0.78	−0.26	0.07		
HIV RNA	0.38	0.02	0.2	0.24	0.35	0.04		
Age at treatment start	0.47	<0.01	0.1	0.35	0.06	0.55		
ART timing	−0.21	0.04	−0.05	0.62	−0.15	0.15		
Factors	IgA				IgG			
	R	P-value	95% CI		R	P-value	95% CI	
CD4 T-cell counts	−0.001	<0.01	−0.002	−0.0004	−0.012	0.021	−0.22	−0.024
Age at treatment start	0.2	<0.01	0.03	0.38				

Abbreviation: ART, antiretroviral therapy.

**Table 3** Correlations between immunoglobulin levels and treatment response by univariate and multivariate analysis through 36 months of treatment

Univariate	IgA				IgM				IgG			
	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI		P-value
Treatment failure	1.69	1.2	2.37	<0.01	1.1	0.47	2.68	0.8	1.19	1	1.4	0.049
Multivariate												
Treatment failure	1.49	1.04	2.12	0.03	0.44	0.05	4.24	0.47	1.22	0.93	1.6	0.15

and switched B cells, and showed that whereas IgM<sup>+</sup>IgD<sup>+</sup> CD27 (IgM only) cells were increased, the switched subset (IgM-IgD<sup>-</sup>) was reduced in viremic individuals. The results suggested that IgM-bearing B cells might not suffer from similar levels of direct and indirect impacts of HIV infection.<sup>32</sup> Similarly, Lugada et al also found that IgM concentrations did not differ between HIV-positive and HIV-negative groups or between CD4-low and CD4-high HIV1-infected children.<sup>20</sup> IgM B cells develop upon encountering thymus-independent antigens or early formation of B-cell response in lymph-node or natural B1 cells, and IgM usually has lower levels of somatic hypermutation compared to IgA and IgG. IgM-producing B cells might not be dependent on CD4 T-cell help, and hence the retained levels of IgM-producing B cells might be reflected in two situations: IgM B cells might not be as affected by CD4 T-cell depletion as switched-memory B cells, and ART can recover IgM B cells at a more profound rate compared to other switched-memory B cells.

There was an inverse correlation between CD4 T-cell counts and IgG levels. Similar findings in other studies include an inverse correlation between IgG memory B cells and CD4 T-cell counts.<sup>20,33</sup> These findings suggested that the quality and quantity of CD4 T cells play an important role

in the differentiation of memory B cells and that the depletion of CD4 T cells might result in uncompleted activation/differentiation of IgG-secreting cells. Others have suggested that cognate T-B-cell interaction might not be necessary for polyclonal B-cell activation,<sup>34,35</sup> and we have found previously that soluble CD27, a marker of immunoactivation, which has been shown to be elevated during HIV infection, might drive activated memory B cells toward plasma differentiation.<sup>8</sup> The increased IgG production might be the consequence of direct or indirect impact via regulation of certain factors. In addition, we observed correlations between IgA levels and CD4 T-cell counts and CD4 T-cell percentage and HIV RNA. Such elevation might occur as the consequence of loss/improper T cell helps and direct consequence of HIV replication.<sup>20</sup>

We observed a significant association between IgG levels and TF by Cox regression analysis, suggesting the important role of IgG levels in monitoring disease progression and treatment response. Studies have shown that hypergammaglobulinemia is one of the hallmarks of HIV infection and that viremic patients tend to produce higher levels of total immunoglobulin than aviremic patients. de Milito et al reported an inverse association between CD4 T-cell counts



and total immunoglobulin levels,<sup>10</sup> implying that total IgG levels might be an indicator of poor immunofunction.

Increased IgA levels were also found to be associated with TF. The mechanism behind such association might be similar to that of IgG, and increased IgA levels might occur as the consequence of increased mucosal immunity. We found that the increased IgG levels were probably due to bystander activation, since the majority of IgG antibodies encountered low specificity. The specificity of IgA has not been studied extensively; however, CD4 T-cell counts in the mucosa were shown to be depleted before the loss of T cells in the periphery. Therefore, we propose that increased IgA levels might also be the consequence of improper T-cell helper and/or bystander activation at mucosal sites. In addition, as the increased microbial translocation occurred during HIV infection, the immune system might respond by producing profound levels of IgA to prevent microbial translocation from the gut lumen to the periphery.<sup>36</sup> However, we observed increased IgA levels in TF patients only, favoring the former hypothesis. Therefore, we suppose that the increased immunoglobulin levels occurred as a consequence of bystander activation of B cells and CD4 T cells. Bystander activation occurs as a consequence of viral replication, which is one of the hallmarks of distortion of the immune system.

The association between IgA levels and treatment response has not been investigated extensively, probably due to the different roles of IgA in the immune system. Our results could be one of the first indicating that IgA levels could be a good marker for monitoring treatment response and that increased IgG and IgA levels occur before decreased CD4 T-cell counts and increased HIV RNA. Therefore, studying alterations in immunoglobulin levels might be beneficial in monitoring treatment response in HIV-infected children.

## Conclusion

In conclusion, elevation of IgG and IgA levels was shown to occur early during HIV infection, and levels were associated with CD4 T-cell counts, HIV RNA, and TF. IgA levels were associated with TF in Cox regression analysis; therefore, monitoring immunoglobulin levels might be beneficial in prognosis of treatment response.

## Acknowledgments

We would like to express our appreciation to the National Foundation for Science and Technology Development, Ministry of Science and Technology, for financial support. We would like to thank our students Dang Minh Diem, Nguyen Manh Tien, Nguyen Huu The Tung, Tran Thi Anh, and Nguyen Anh Dung for their valuable contribution.

## Author contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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