Clinical Immunology (2015) 157, 26–29

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

LETTER TO THE EDITOR

HLA-DRB1454 and predictors of new-onset asthma in HIV-infected Thai children☆

KEYWORDS
Asthma;
HIV-infected children;
Antiretroviral therapy

To the Editor

Recent cohort studies have demonstrated a rise in asthma incidence following antiretroviral therapy (ART) in US children living with HIV [1–3], possibly due to immune reconstitution [2]. As the extent of immune reconstitution can be affected by the pre-ART CD4 level, we assessed new onset asthma in a randomized study of children who initiated ART at different CD4 levels in the Pediatric Randomized Early versus Deferred Initiation in Cambodia and Thailand study (The PREDICT study) [4]. We hypothesized that children who initiated ART early will have higher CD4 and higher incidence of asthma. We also aimed to identify genetic and immunologic predictors of new onset asthma.

In brief, from 2006 to 2011, the PREDICT study included ART-naive HIV-infected Thai and Cambodian children, aged 1–12 years, with CD4 15–24% and no CDC (Center for Disease Control and Prevention) clinical category C who were randomized to either immediate-ART or deferred-ART when CD4 declined to <15% and followed them for 144 weeks. For this analysis, only data from Thai children were included for consistency of available data. Children previously diagnosed with asthma or other chronic lung conditions were excluded. Diagnosis of asthma was defined as asthma medication use after age ≥3 years (e.g. bronchodilators, and inhaled corticosteroids) [1]. The data were censored at the time of randomization and asthma incidence was reported thereafter.

Human Leukocyte Antigen (HLA)-B and HLA-DR with four-digit specificities were determined using Hiseq single-end sequencing of the amplicon/high resolution technique by Bejing Genomic Institute — Hongkong Co., Limited, Hong Kong [5]. Flow cytometry was performed at baseline by methods previously described for the following cell subsets: activated CD4 ($CD4^+38^+DR^+$) and activated CD8 ($CD8^+38^+DR^+$) T cells [6]. C Reactive Protein (CRP) was measured using the CRP High Sensitive Assay (Cobas Integra System, Roche Diagnostic Systems, Basel, Switzerland).

Statistical analysis was conducted with Stata version 12.1 (Statacorp, College Station, TX, USA). Cox Proportional Hazards regression was used to determine the independent predictors of asthma. Multivariate analysis included covariates significant from the univariate analysis having a $P \leq 0.1$. The p-values < 0.05 were considered statistically significant.

Of 179 children, 165 were included in this analysis (83 from the immediate-arm and 82 from the deferred-arm). Fourteen were excluded for previously diagnosed asthma (11) and chronic lung disease [1] before enrollment, loss to follow-up at week 0 [1] and ART use prior to entry [1]. All children were perinatally HIV-infected with a baseline median (IQR) age of 7.5 (4.8–9.0) years, and 62% were female. The most common ART regimen was zidovudine/lamivudine/nevirapine (91%). All immediate-arm children had 144 weeks of ART. Thirty-one (38%) children in the deferred-arm initiated ART and had a median (IQR) duration of HAART of 78 (45–118) weeks. At week 144 (end of study), children from the immediate-arm had higher median CD4% (32% vs. 23%), CD4 count (905 vs. 567) cells/mm^3, and lower HIV-RNA (1.7 vs. 3.8) log_{10}-copies/ml when compared to the deferred-arm (all $p < 0.001$).

The rate of new onset asthma in the immediate-arm was 26.5% compared to 17.1% in the deferred-arm ($p = 0.14$). At time of asthma diagnosis, there was a trend towards higher CD4% in the immediate-arm (26.3%) compared to the deferred-arm (21.4%) ($p = 0.07$). The median time between baseline and onset of asthma was 11 weeks in the immediate-arm and 24 weeks in the deferred-arm ($p = 0.16$). The asthma medications used were oral/inhaled salbutamol (75%), oral terbutaline (12.5%), and others (i.e. inhaled

☆ This study was presented as a poster presentation (P_56) at the 5th International Workshop on HIV Pediatrics, Kuala Lumpur, Malaysia, 28–29 June 2013. The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.

Abbreviations: ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; HLA, human leukocyte antigen; PREDICT, the Pediatric Randomized Early versus Deferred Initiation in Cambodia and Thailand study.

http://dx.doi.org/10.1016/j.clim.2014.12.006

Table 1 Predictors of new onset asthma in HIV-infected Thai children.

	Univariate				Multivariate			
	HR	95% CI		P	HR	95% CI		P
		Lower	Upper			Lower	Upper	
Age > 6 years	1.02	0.91	1.14	0.73				
Female vs. male	0.9	0.47	1.72	0.74				
CDC classification B vs. N/A	1.79	0.94	3.43	0.08	1.65	0.84	3.25	0.15
Child lived in orphanage	0.7	0.29	1.67	0.42				
Monthly income of primary caregivers				0.02				0.03
Average income or above	1	–	–		1	–	–	
Unknown income	1.99	0.76	5.22		1.93	0.69	5.35	
Very or low income	2.74	1.15	6.52		2.70	1.11	6.53	
Weight for age z-score < −2.0	1.76	0.82	3.74	0.14				
Height for age z-score < −2.0	1.79	0.92	3.48	0.09	1.61	0.80	3.23	0.18
Immediate vs. deferred-arm	1.72	0.89	3.33	0.10	2.16	1.07	4.36	0.03
Baseline CD4 < 20%	1.14	0.6	2.18	0.70				
Baseline HIV-RNA $\geq 5\log_{10}$copies/mL	1.59	0.81	3.13	0.18				
Activated T helper cell	0.98	0.93	1.03	0.37				
Activated cytotoxic T cell	1.02	0.99	1.05	0.28				
CRP > 1 mg/dl	1.45	0.65	3.2	0.36				
HLA-B4601	2.19	1.1	4.34	0.03	1.82	0.84	3.94	0.13
HLA-DRB1454	3.95	1.62	9.61	0.002	3.73	1.42	9.82	0.01

budesonide, unspecified oral/inhaled bronchodilator, and salbutamol + budesonide) (12.5%). Median (IQR) durations of medications use were 16 (10–41) days for salbutamol, 7 [5–8] days for terbutaline, 167 (34–427) days for budesonide, and 5 [2–6] days for bronchodilator with no differences between arms (all $p > 0.2$).

A higher proportion of children who were diagnosed with asthma had HLA DRB1454 expression compared to those without asthma; 22.2% (8/36) vs. 9.3% (12/129), respectively ($p = 0.03$). The other alleles were not predictive of asthma. Similarly, levels of CRP and frequencies of activated CD4 and CD8 T cells were not associated with asthma diagnosis.

By multivariate analysis, predictors for asthma were immediate ART (HR 2.16, 95% CI 1.07–4.36), living in low-income household (HR 2.7, 95% CI 1.11–6.53) and HLA DRB1454 (HR 3.73, 95% CI 1.42–9.82) (Table 1).

In this study, the immediate ART was associated with higher CD4 and asthma. In fact, the incidence of asthma in the immediate-arm (26.5%) exceeded those that were seen in healthy Thai children (18%) [7]. Together with other reports [1,2], these data support the contribution of immune reconstitution on the development of asthma following ART initiation. Low household income and HLADRB1454 were also predictive of asthma. Low income status was associated with poor asthma control in African American youths [8]. In HIV-infected US children, HLA-A68 was associated with asthmatic medication use while HLA-Cw6 was a preventive factor [9].

The randomized nature of our study is a strength but there are many limitations. The study is underpowered and spirometry was not done. The asthma medication use could have been for non-asthma indications such as viral respiratory infections. However, with one in five children experiencing new onset of asthma after ART, these data convey the need for health care providers to be vigilant in identifying new asthma diagnosis in children who initiate ART.

Acknowledgments

The PREDICT study is sponsored by National Institute of Allergy and Infectious Disease (NIAID), Grant number U19 AI053741 and Clinical trial.gov identification number NCT00234091. Antiretoviral drugs for PREDICT are provided by GlaxoSmithKline (AZT, 3TC), Boehringer Ingelheim (NVP), Merck (EFV), Abbott (RTV) and Roche (NFV). The study is partially funded by the National Research Council of Thailand. We are grateful to the children and their families for participating in PREDICT.

The list of the investigators, clinical centers, and committees participated in the Pediatric Randomized of Early versus Deferred Initiation in Cambodia and Thailand (the PREDICT study) was in online repository.

Below list is for the online supplement.

List of the investigators, clinical centers, and committees participated in the Pediatric Randomized of Early versus Deferred Initiation in Cambodia and Thailand (PREDICT)

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