Frequency and magnitude of HIV viral blips in HIV treatment-experienced children are associated with a decline in CD4+ T-cells over time

Authors: Elijah Paintsil, MD[¥*], Ryan Martin[ǂ*], Ariel Goldenthal[¶], Shreya Bhandari[±], Warren Andiman, MD[†], Musie Ghebremichael, PhD[‡]

From the [¥]Departments of Pediatrics and Pharmacology, Yale University School of Medicine, New Haven, CT; [ǂ]Columbia University College of Physicians and Surgeons, New York, NY; [¶]Georgetown University, Washington, DC; [±]Tufts University, Medford, MA; [†] Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [‡]Ragon Institute and Harvard Medical School, Cambridge, MA.

Correspondence to: Musie Gebremichael, PhD, Ragon Institute and Harvard Medical School; 400 Tech Square, Room 857, Cambridge, MA 02129, musie_ghebremichael@dfci.harvard.edu

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Running head: Viral blips in HIV-infected children

[*]EP and RM, equal contribution

Abstract

The clinical consequences of viral blips in HIV-infected children are not known. We examined the predictors and immunologic consequences of viral blips in 104 HIV-infected children. Over 80% (N=86) of the children had detectable viral load (HIV RNA viral load ≥50 copies/ml) in more than 50% of their available viral loads. Children with infrequent viral blips had significantly higher CD4+ T-cell counts overtime compared to those with frequent viral blips (P<0.0001). Both frequency and magnitude of viral blips had effect on CD4+ T-cells. Strict adherence to a treatment goal of undetectable HIV viremia in children is likely to be beneficial.

Keywords: HIV-infected children, CD4+ T-Cell, viral blips.

Introduction

The management of the pediatric HIV epidemic is one of several HIV success stories; however, mother-to-child transmission (MTCT) of HIV continues to fuel the pediatric HIV epidemic particularly in resource-limited countries [1]. In 2012, there were 260 000 (230 000 – 320 000) new HIV infections in children under 15 years of age (UNAIDS: Global Fact Sheet 2013). Antiretroviral therapy (ART) coverage in children is low; the goal of ART is to suppress HIV viral replication and restore immune function (i.e., CD4+ T-cell recovery). Uncontrolled HIV viremia leads to depletion of CD4+ T-cells with a concomitant increase in risk for opportunistic infections, AIDS, and death [2-4].

HIV RNA levels vary in individual patients; this variation is greater in children than in adults [5-7]. HIV RNA >500 copies/mL after having formerly achieved virologic suppression is generally accepted as virologic failure [8-10]. However, isolated episodes of plasma HIV RNA >500 copies/mL (i.e., transient viremia) followed by return to levels of viral suppression often observed in adults and children on ART are not considered as virologic failure [8, 11, 12]. Transient viremia is relatively common among children on ART [11, 13]. The underlying mechanisms and clinical consequences of transient viremia or "viral blips" are debatable. A number of mechanisms have been implicated, including variable sensitivity of viral load assays [14], random statistical and biological variations [15], opportunistic infections [16], activation of latently infected cells [17], non-adherence to ART [18], and evolution of drug resistant viruses [19, 20]. The clinical significance of transient viremia or viral blips has evoked mixed reports. While some studies have reported that viral blips are of no clinical significance [15, 21, 22], others

studies have reported an association between viral blips and virologic failure [8, 23, 24], depletion of CD4+ T-cells [25], and emergence of drug resistant viruses [19, 20].

There is a paucity of data on the clinical significance of viral blips in children. The higher variability and natural age-associated decline of CD4+ T-cells seen in children may limit the extrapolation of findings of clinical significance of viral blips in adults to children [26]. The main objectives of our study were to examine the predictors of viral blips and the association between viral blips and CD4+ T-cell changes over time in children.

Materials and Methods

Study participants: Longitudinal data were extracted from the Yale Prospective Longitudinal Pediatric Cohort study at Yale-New Haven Hospital. The rationale, organization, and recruitment of the subjects for the cohort study have been described previously [27]. The study was reviewed and approved by Yale School of Medicine Human Investigation Committee.

Study Variables: The outcome variables of the study were absolute CD4+ T-cell count and HIV-1 viral load. The predictor variables included, gender, race, age at study entry, age at HIV diagnosis, caregiver type, history of AIDS defining illness, time since HIV diagnosis, CDC clinical staging of HIV infection, and baseline CD4 T-cell count.

Definitions: Viral blip was defined as any detectable viral load above the limit of detection offered by the assay [28]; we used either 50 or 500 copies/mL as the cutoff viral load. The study participants were divided into two categories based on their frequency of viral blips: *Infrequent blips*: this category comprised individuals who had viral blips in

fewer than 50% of their clinical visits. *Frequent viral blips:* this category comprised individuals who had ≥ 50% viral blips of their clinical visits.

Clinic and follow-up visits

The study participants were seen and examined at the pediatric specialty clinic every three to four months and more frequently as necessary. Since 1996, HIV-1 RNA quantification and CD4+ T- cell counts and percentages were done at every clinic to follow HIV disease progression. The Amplicor Monitor™ test (Roche Diagnostic Systems, Inc., Branchburg, New Jersey, USA) was used for the quantification of the HIV-1 RNA, in accordance with the manufacturer's instructions and the AIDS Clinical Trials Group (ACTG) quality assurance recommendations were followed, as described elsewhere [29]. The assay's detection limit was 400 copies/mL and 50 copies/mL, before 2004 and after 2004, respectively. CD4+ T-cells were quantified by standard dual-platform flow cytometry technology by a certified clinical laboratory at Yale-New Haven Hospital.

Statistical Analysis: Descriptive measures were used to summarize the data. Continuous variables were summarized using median and inter quartile range (IQR); categorical variables were summarized using frequency and percent (%). Wilcoxon rank sum and Fisher's exact tests were used to compare continuous and categorical variables, respectively, between subjects with rare and frequent viral blips. Regression analyses using logistic regression models were used to estimate the odds of having frequent viral blips. Longitudinal data analyses using polynomial random coefficients models were conducted to examine differences in CD4+ T-cell counts by viral blips. Two-sided p-values are reported for all the statistical tests used in the analysis.

Results

One hundred and four (104) HIV-infected children with more than one HIV viral load measurement between 1996 and November 2013 were included in the analysis. The demographic and HIV disease characteristics of the study participants are described in Table 1. Fifty four percent were males, 59% were African Americans, and 57% had biological parents as caregivers. The majority of the participants had congenital HIV (93%), moderate to severe CDC classification (65%), and other comorbidities (55%).

The study participants were divided into two categories based on the frequency of viral blips over the study period. The 'infrequent blip' category comprised individuals who had fewer than 50% of viral loads above the detection limit of the assay. The 'frequent blips' category comprised individuals who had detectable viral load in more than 50% of their viral loads. When blips were defined as viral loads ≥50 copies/ml, more than 80% (N=86) of the children had frequent viral blips during the course of the study. Table 1 shows the characteristics of the study population stratified by viral blips category. There were no statistically significant differences in patient characteristics between the two viral blips categories.

Figure 1A displays the odds of having frequent blips with corresponding 95% confidence intervals. Although race/ethnicity, baseline CD4+ T-cell count, and time since diagnosis did not reach statistical significance, they were associated with the frequency of viral blips. The odds of having frequent blips was 34% (OR=1.34, 95% CI: 0.44-4.06) higher in black children compared with children from other races. Moreover, the odds of having frequent viral blips diminished by 21 % (OR=0.79, 95% CI: 0.48-1.30) in children

with higher baseline CD4+ T-cell count (per 1-SD increase in baseline CD4 counts) compared with children with lower baseline CD4+ T-cell count.

Individual growth models were used to explore participant's longitudinal CD4+ T-cell data over time. Figure 1B displays the empirical growth plot of CD4+ T-cell data with average trend lines (smooth) included for the two viral blips categories. The trend lines show that the CD4+ T-cell values for both groups slowly increased at earlier and decreased at later points over the study period. Since the trend lines were curvilinear, a quadratic random coefficients model was applied. The likelihood ratio test indicated that the quadratic model fits the data better than the linear model ((χ^2 =461, df=9-6, P<0.0001) and hence results of the quadratic model are reported here. Children with infrequent viral blips had significantly higher CD4+ T-cell counts over time compared with those with frequent viral blips (P<0.0001). The mean square root of the CD4+ T-cell count since HIV diagnosis was 29.13 (95% CI:25.43-32.85) cells/mm^3 in the infrequent viral blips group and 20.05 (95% CI: 18.43-21.66) cells/mm^3 in the frequent blips group. The rate of change in CD4+ T-cell count depended on time in both groups: $2.43 - 0.25T$ in the infrequent viral blips group and $0.52 - 0.07T$ in the frequent viral blips group, where, T denotes time from HIV diagnosis. Though the rate of change of the average CD4+ T-cell count over time was not statistically different between the two groups (p=0.10), the rate was higher in the infrequent blips category. We also conducted a sensitivity analysis using a viral blips definition with a cutoff of 500 copies/mL. This definition is more reflective of individuals with frequent and persistent viremia between 50 to 500 copies/mL. The findings from our sensitivity analyses were identical to that reported above using 50 copies/mL as cutoff (data not shown).

Discussion

We found that viral blips were common in our pediatric cohort. Of the 104 HIV-infected children who were enrolled in the study, more than 80% (N=86) had frequent blips (>50 copies/mL) during the course of the study. Moreover, there was an inverse relationship between frequency of viral blips and CD4+ T-cell trajectory. None of the demographic or clinical characteristics of participants was significantly associated with viral blips. The odds of having frequent blips were 30% higher in black children compared with children from other ethnicities. Higher baseline CD4+ T-cell count was associated with less frequent viral blips. Throughout the study period, children with infrequent viral blips had significantly higher CD4+ T-cell counts.

Our finding of inverse correlation between frequency of viral blips and CD4+ T-cell is consistent with findings from previous studies in adults [25, 30-32]. Boufassa et al reported that viral blips in HIV controllers were associated with a significant decline in CD4+ T-cells [25]. Di Mascio et al reported a negative correlation between frequency of viral blips and baseline CD4+ T-cell counts [30]. Martinez et al observed that patients with frequent viral blips had lower CD4+ T-cell counts after 12 and 18 months of therapy [31]. They also reported that the frequency rather than the magnitude of the blips was associated with impaired CD4+ T-cell count recovery. We observed that both frequency and magnitude of viral blips had an effect on CD4+ T-cells. Interestingly, other studies have reported that viral blips predate virologic failure [8, 23, 24]. Virologic failure often results in faster decline of CD4+ T-cells and subsequent AIDS-related clinical events [25].

Our findings have implications for pediatric ART monitoring in both resource-rich and resource-limited countries. In general, HIV-infected children are less likely than infected adults to achieve full viral suppression on ART [33-35]. Viral load monitoring is not routine in resource-limited countries. The 2013 WHO HIV treatment guidelines define virologic failure as plasma viral load above 1000 copies/mL on two consecutive measurements three months apart in individuals adherent to medication use (www.who.int/hiv). This cutoff may be too high, thereby leading to high prevalence of virologic failure and subsequent CD4+ T-cell decline. Moreover, early virologic failure may be missed, resulting in evolution of drug resistant HIV variants in HIV-infected children in sub-Saharan Africa [36, 37]. Further studies on the clinical significance of viral blips in HIV-infected children are needed to inform appropriate cutoffs for virologic failure.

Our study has several strengths compared with previous studies. It is a large population-based study, enhancing its generalizability and it is one of the few studies on viral blips in children. However, the study has several limitations. First, it spans a period of nineteen years during which time HIV medicine underwent rapid and complex changes in treatment regimens. Since these changes were not envisaged at the inception of the cohort study, critical treatment data are missing, making it difficult to assess the direct impact of the components of various regimens on viral blips and CD4+ T-cell counts. Also, viral blips during non-adherence may have different consequences from blips during complete adherence [8]. Second, our definition of viral blips is arbitrary and conservative; however, in the absence of a consensus on the definition of viral blips, our findings are consistent with other studies using various definitions of viral blips.

In conclusion, strict adherence to ART with the goal of undetectable HIV viremia in children is likely to be beneficial. Repeated viral loads above the detection limit of the assay may lead to unintended persistent viremia with subsequent virologic failure, decline in CD+ T-cell count, and evolution and spread of drug resistant HIV variants.

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Disclosure

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Table 1. Characteristics of study participants stratified by frequency of viral blips

	All (N=104)	**Blip**		**P-value**
		Infrequent (N=18)	**Frequent (N=86)**	
Study covariates				
	Median (IQR)			
Baseline CD4 /mm^3	436 (125-725)	550 (26-820)	420 (140-663)	0.48
Baseline VL (Log_{10})	4.79 (4.13-5.32)	4.60 (2.60-5.50)	4.79 (4.20-5.18)	0.85
Age at study entry (years)	7.83 (5.02-11.98)	7.74 (3.70-13.07)	7.83 (5.20-11.76)	0.92
Age at diagnosis (years)	1.79 (0.44-4.91)	2.04 (0.21-5.32)	1.79 (0.52-4.91)	0.82
Time since Diagnosis (years)	5.14 (2.32-7.35)	3.03 (0.60-8.88)	5.42 (2.52-7.32)	0.40
	N (%)			
Gender				1.00
Female	48 (46%)	8 (44%)	40 (47%)	
Male	56 (54%)	10 (56%)	46 (53%)	
Race/Ethnicity				0.80
Black	61 (59%)	10 (56%)	51 (59%)	
Other	43 (41%)	8 (44%)	35 (41%)	
Other Illness				1.00
No	43 (45%)	7 (47%)	36 (44%)	
Yes	53 (55%)	8 (53%)	45 (56%)	
Caregiver				0.79
Parent	59 (57%)	11 (61%)	48 (56%)	
Other	44 (43%)	7 (39%)	37 (44%)	
Mode of transmission				
Congenital	97 (93%)	15 (83%)	82 (95%)	0.10
Other	7 (7%)	3 (17%)	4 (5%)	
CDC Classification				0.37
N: None	14 (13%)	4 (22%	10 (12%)	
A: Mild	23 (22%)	3 (17%)	20 (23%)	
B: Moderate	30 (29%)	3 (17%)	27 (31%)	
C: Severe	37 (36%)	8 (44%)	29 (34%)	

Figures

Figure 1A: Risk factors for viral blips among children in Yale-New Haven Hospital

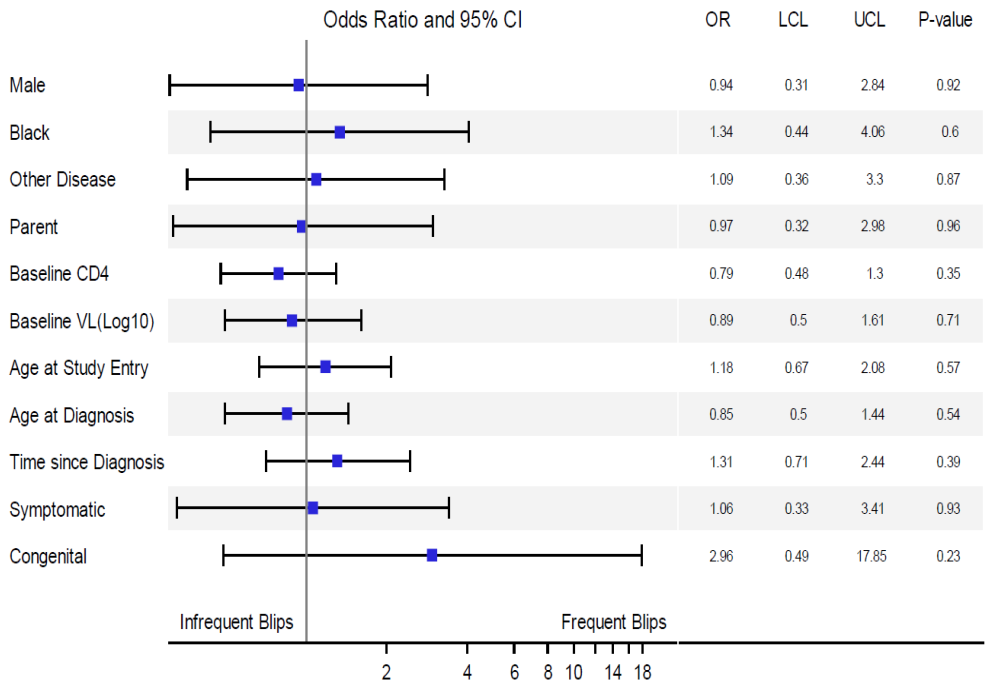

Figure 1B: CD4+ T-cell count trajectories by blip status among children in Yale-New Haven Hospital