Long-term HIV reservoir dynamics in early treated Thai children

Marta Massanella[1,*], Amélie Pagliuzza[1], Caroline Dufour[1], Thidarat Jupimai[2], Supranee Buranapraditkun[3], Rapisa Nantanee[2,4], Julie Mitchell[5], Mark de Souza[6], Piyarat Suntarattiwong[7], Lydie Trautmann[8,9], Rémi Fromentin[1], Thanyawee Puthanakit[2,4,10], Nicolas Chomont[1]; on behalf of the HIVNAT209 study group

[1]Centre de Recherche du CHUM and Department of Microbiology, Infectiology and Immunology, Université de Montréal, Montreal, Canada; [2]Center of Excellence in Pediatric Infectious Diseases and Vaccines, Chulalongkorn University, Bangkok, Thailand; [3]Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [4]Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [5]Vaccine and Gene Therapy Institute, Oregon Health & Science University, Beaverton, OR, USA; [6]SEARCH Research Foundation, Bangkok, Thailand; [7]Queen Sirikit National Institute of Child Health, Bangkok, Thailand; [8]U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD; [9]Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD ; [10]The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), the Thai Red Cross AIDS Research Centre (TRC-ARC), Bangkok, Thailand

mmassanella@irscaixa.es
nicolas.chomont@umontreal.ca

1030

BACKGROUND

- Early antiretroviral therapy (ART) and continuous suppression drastically limit the size of the HIV reservoir in adults.
- However, long-term follow up data on the size and composition of the reservoir in children who initiated ART during the first weeks of life remain limited.

AIM

To study the effect of early ART on the long-term dynamics of HIV reservoir markers in Thai children suppressed on ART for up to 10 years.

METHODS

- **Study cohort:** Forty-nine children with perinatal HIV who initiated ART within a median of 10 IQR [5-14] weeks of life were followed annually (up to 9.9 years). All children received continuous ART during the follow-up period.
- **Total and integrated HIV DNA:** Total (LTR-gag) and integrated (LTR-Alu) were quantified in CD4 T cells by qPCR.
- **Inducible HIV reservoir** was measured by Tat/rev Induced Limiting Dilution assay (TILDA). CD4 T cells were enriched from PBMCs, and the frequency of CD4 T cells producing multiply spliced RNA (msRNA) was quantified following stimulation with PMA/ionomycin.
- **Statistical Analysis:** Mixed-effects models were used to measure longitudinal decays in each HIV reservoir marker. Phase 1: 0-1.23 years and phase 2: >1.23 years and after

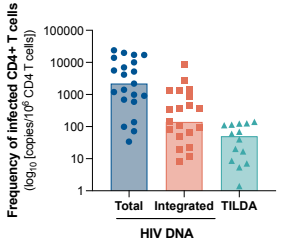
Table 1. Characteristics of the cohort

	Longitudinal n = 49
Gender, female, n (%)	23 (47)
HIV transmission, n (%)	
In utero	15 (31)
Peripartum	19 (39)
Unknown	15 (31)
Prophylactic ARV history, n (%)	
None	3 (6)
AZT	9 (18)
AZT+3TC+NVP	37 (76)
Direct transition from prophylactic ARV to ART	20 (41)
Duration prophylactic ARV, days, median [IQR]	33 [28-44]
Age of ART initiation, months, median [IQR]	2.3 [1.2-3.4]
Age at first study visit, years median [IQR]	1 [0.2-1.3]
Age at last study visit, years median [IQR]	5 [2.8-7.4]
Continuous suppresion, <50 HIV RNA copies/ml, n (%)	50 (100)
Time on ART at first study visit, years, median [IQR]	0.9 [0-1.1]
Time on ART at last study visit, years, median [IQR]	4.9 [2.7-7.3]
Longitudinal follow up:	
>5 years on ART, n (%)	25 (50)
>6 years on ART, n (%)	18 (36)
>7 years on ART, n (%)	14 (28)
>8 years on ART, n (%)	10 (20)
>9 years on ART, n (%)	7 (14)
ART regimen, First Visit	
PI-based	47 (94)
NNRTI-based	3 (6)

1. Early ART initiation in vertically infected Thai infants leads to a rapid initial decline in HIV reservoirs, followed by a stable second phase.

2. Prolonged treatment is associated with a progressively lower proportion of children having a detectable inducible reservoir over time.

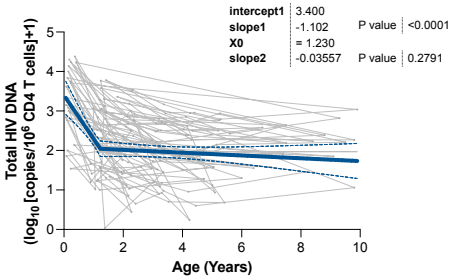
RESULTS



- Total HIV DNA, integrated HIV DNA and inducible reservoir were detected in all children at high levels before ART initiation

Figure 1. Total and integrated HIV DNA and inducible reservoir (TILDA) before ART initiation

A. Total HIV DNA



B. Integrated HIV DNA

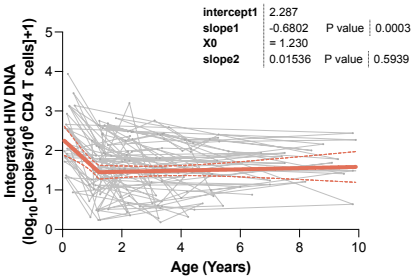
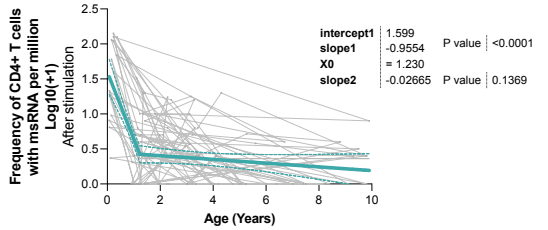
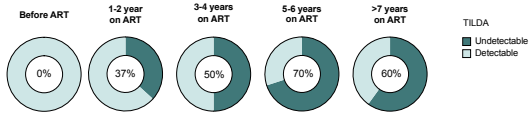


Figure 2. Longitudinal analysis over a median 4.9 IQR [2.9-7.3] years of ART of Total (**A**) and Integrated (**B**) HIV DNA, and Inducible reservoir (TILDA), **C**). Frequency of samples with undetectable inducible reservoir as measured by TILDA during the study period (**D**). Slopes from 1st and 2nd phase decay for all reservoir markers (**E**)

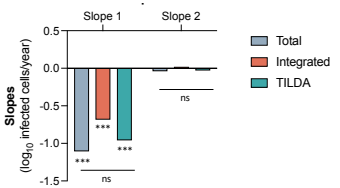
C. Inducible HIV reservoir



D. Proportion of Samples with Undetectable TILDA Over Time



E. Slopes of HIV reservoir markers



Slope 1: All slopes from the three reservoir slope markers are significantly different from 0 (P < 0.0003 for all cases), but no significant differences are observed among them (P = 0.25).

Slope 2: None of the slopes from the three reservoir slope markers differ significantly from 0 (P>0.05), and no significant differences are observed among them (P = 0.4).

- All HIV reservoir markers showed a biphasic decay: a rapid initial decline with similar half-lives between markers, followed by stabilization.
- Despite no apparent decrease in the size of inducible reservoir, the proportion of participants with detectable TILDAs decreased with time on ART: TILDA+ cells were detected in all children at baseline (100%, n=14), in 60% after 1 to 3 years on ART (n=62), and in less than 40% of the participants after 4 years of therapy (n=32).

CONCLUSIONS

- A large pool of HIV-infected cells is rapidly established in vertically infected Thai infants. Early ART initiation (within 3 months of life) is associated with a rapid initial decay of all HIV reservoir markers, followed by a stable second-phase.
- The proportion of children with detectable inducible reservoir as measured by TILDA continues to decrease after 3 years on ART, suggesting that prolonged therapy may have long-term benefits in this population.

ACKNOWLEDGEMENTS

The funding statement is "This Research is funded by Thailand Science Research and Innovation Fund Chulalongkorn University (HEAF67300088)