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Proviral HIV-1 DNA Below Detection in Early Treated Adolescents and Prior Treatment Interruptions

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BACKGROUND

Undetectable or low HIV-1 DNA levels have been associated with a greater likelihood of ART-free viral control in adults treated during primary infection. Here we investigate predictors of HIV-1 DNA levels in a cohort of early-treated children and adolescents recruited on characteristics expected to make them good candidates for future remission/cure trials.

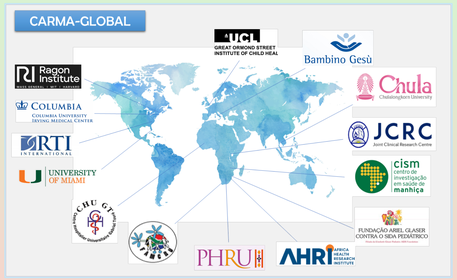


Figure 1. CARMA-GLOBAL study sites.

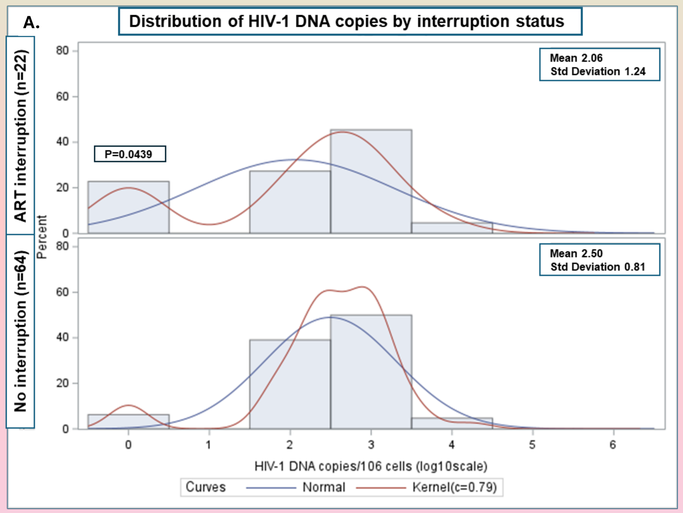
METHODS

Parents or guardians of children and adolescents with perinatally-acquired HIV starting ART <3 months of age, >7 years prior and with plasma HIV-1 RNA <50 copies/ml on ART were recruited at 8 sites in South Africa, Mozambique, Uganda, Mali and Thailand (Figure 1, 2). Children who had undergone ART interruptions for any reason could also enroll if ART had been resumed for >2 years. HIV-1 DNA was measured in total PBMCs using droplet-digital PCR. Associations between DNA levels and prior factors were investigated with descriptive statistics and chi-square tests.



Figure 2. CARMA-GLOBAL study teams A. Chulalongkorn University, Thailand. B. Michael Mapongwana Community Clinic, Khayelitsha C. FAMCRU, Tygerberg Hospital, Cape Town, South Africa E. JCRC, Kampala, Uganda. F. Data Coordinating Center, PHRU, Soweto, South Africa.

Approximately 10% of children and adolescents who had started ART under 3 years of age and who were well suppressed on ART for at least 7 years had HIV-1 DNA levels below the assay's detection threshold.
In this group, history of ART interruption was associated with a *greater* likelihood of undetectable HIV-1 DNA.



B. **ART INTERRUPTION GROUP (N=22)**

Age at ART interruption (years) Median (p25-p75)	1.38 (0.92-2)
Duration of ART interruption (months) Median (p25-p75)	2.44 (1.23-5.24)
Time on ART after interruption (years) Median (p25-p75)	15.08 (8.13 -16.13)

Figure 3. A. Histogram of the distribution of HIV-1 DNA copies/mill cells (log 10 scale) in children with ART interruption (above) and children with no ART interruption (below). B. Characteristics of children with ART interruption.

RESULTS

ART was started at a median of 65 days (IQR 52-85) among 87 participants (49.4% male) enrolled in this study at a median age of 13.2 years of age (IQR 9.6-16.7).

Overall, the median HIV-1 DNA level was 340 copies/10^6 cells (IQR: 145- 909) and 10.3% were below the threshold of detection (<1 copy/10^6 cells). Distributions of HIV-1 DNA did not differ between male and female participants; and, within this truncated range of age of ART start, those starting ART <60 days of age had HIV-1 DNA median 240 copies/ 10^6 cells (IQR 83-873; 12.8% undetectable) similar to those starting >60 days: median 396 copies/10^6 cells (IQR 208-943, 8.3% undetectable).

Undetectable HIV-1 DNA was more frequent in those who had undergone ART interruption (22.7%) than those on continuous ART (6.3%) p=0.04 (Figure 3A).

Median age of ART interruption was 1.4 years, with about half interrupting by study design, and the median duration of interruption was 2.4 months (Figure 3B). There were no differences in the age of starting ART or sex distribution between those who did and did not interrupt.

CONCLUSIONS

Around 10% of early-treated children and adolescents well-suppressed on ART for more than a decade had HIV-1 DNA levels below the assay's detection threshold. Having undergone a prior ART interruption was associated with greater likelihood of undetectable HIV-1 DNA. These results provide intriguing support for the concept of "auto-immunization," where repeat cycles of ART interruption are undertaken to bolster HIV immunity toward ART-free viral control.

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