DIFFERENCES IN THE INDUCED LATENT HIV RESERVOIR IN PERINATAL AND ADULT INFECTIONS

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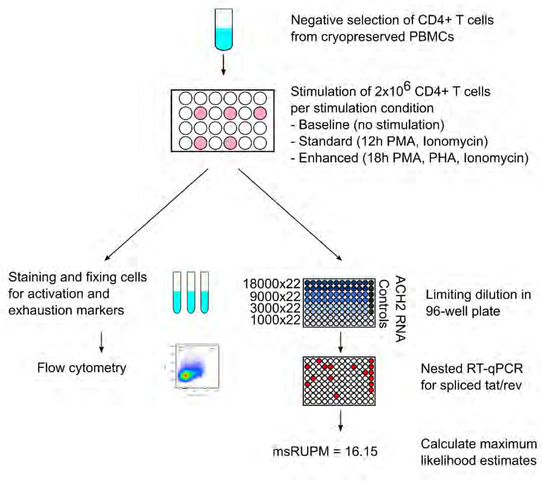
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BACKGROUND

- The latent HIV reservoir in resting memory CD4+ T cells forms a barrier to cure, and is protected from immune- and antiretroviral-mediated clearance
- The tolerogenic and epigenetic profiles of the immune landscape during reservoir establishment in perinatal compared with adult HIV infection may influence HIV reactivation under T-cell activation conditions.
- Reactivation of HIV from latency, as a way to eradicate the reservoir, is a key component of HIV eradication trials in adults; defining the potential for latency reversal in perinatal HIV infection is critical for informing application of this therapeutic approach to perinatal infection

METHODS

- CD4+ T cells were obtained from adolescents (N=11; median age 15.8 yrs) living with perinatally-acquired HIV infection and adults (N=10; median age 40.5 yrs) with horizontally-acquired infection and who had effective virologic suppression with ART for >1 yr.
- The induced proviral reservoir size in CD4+ T cells was determined using a modified the Tat/rev Induced Limiting Dilution Assay (TILDA) developed by Procopio et al.[2]
- The total and intact proviral HIV DNA reservoir was measured by a GAG-LTR ddPCR assay and the Intact Proviral DNA Assay (IPDA)[1].
- Immune activation was assessed by flow cytometry.



The latent HIV reservoir in perinatal infection is **less permissive to latency reversal** compared to adult infections as measured by multiply-spliced HIV RNA.

RESULTS

- Despite similar rates of T cell activation with PMA/ionomycin, the latent reservoir in perinatal infection is slower to reactivate and of lower magnitude compared to adult infection, independent of proviral load.
- An enhanced TILDA with the addition of phytohemagglutin and for 18 hours augmented proviral expression in perinatal but not adult infection.
- Baseline HLA-DR+ CD4+ T cells was significantly lower in perinatal compared with adult infections, but not correlated with induced reservoir size.

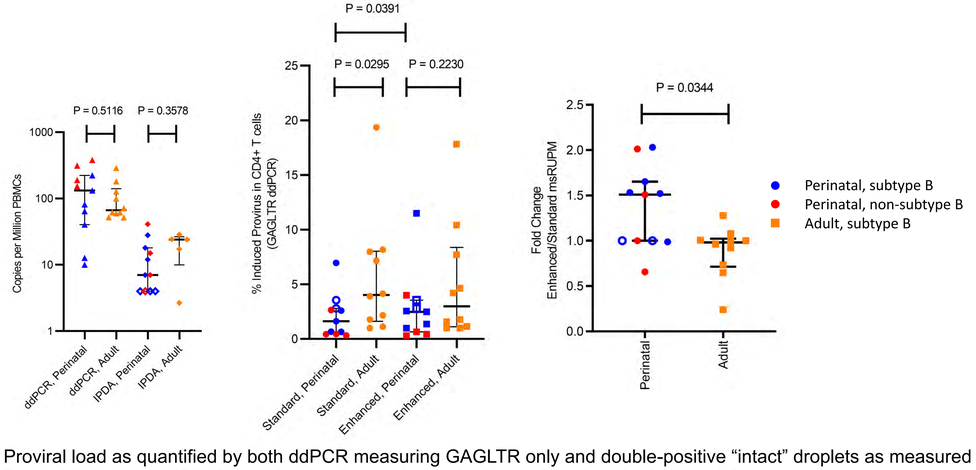


Figure 1: Proviral load as quantified by both ddPCR measuring GAGLTR only and double-positive "intact" droplets as measured by the Intact Proviral DNA Assay (IPDA)**. Proviral load was similar in the perinatal and adult participants.**
Figure 2: Percentage of proviruses in CD4+ T cells that were induced under Standard and Enhanced TILDA conditions in perinatal and adult infections, normalized to GAGLTR copies per calculated CD4+ T cells. **Significantly lower inducibility of proviruses was found in perinatal compared with adult infections.**
Figure 3: Fold change in the size of the inducible reservoir with the Enhanced stimulation condition in perinatal and adult infections. **The enhanced stimulation condition led to a 1.5-fold increase in the induced reservoir in perinatal infection.**

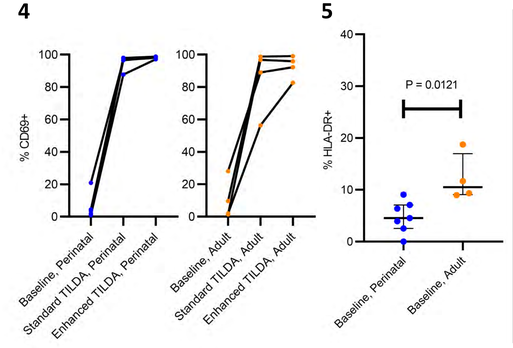


Figure 4: Percentage of CD4+ T cells displaying the activation markers CD69 during baseline, Standard and Enhanced TILDA stimulation conditions in perinatal (left) and adult (right) infections.

Figure 5: Baseline levels of the activation marker HLA-DR between perinatal and adult infections as measured by flow cytometry.

CONCLUSIONS

- The induced latent reservoir for HIV in CD4+ T cells of adolescents with perinatal infections on long-term effective ART was significantly more resistant to reactivation compared to adults.
- Participants in this study had similar proviral loads and rates of cellular activation in response to stimulation.
- At baseline, the median proportion of CD4+ T cells expressing HLA-DR was significantly higher in the adult-acquired infection compared with perinatal infections.
- This has implications for latency reversal strategies towards reservoir clearance and remission in the pediatric population.

ADDITIONAL KEY INFORMATION

Publication: Dhummakupt A, Rubens JH, Anderson T, Powell L, Nonyane BA, Siems LV, Collinson-Streng A, Nilles TL, Jones RB, Tepper V, Agwu A, Persaud D. Differences in the induced latent HIV reservoir in perinatal and adult infection. 2020 Jan 30. JCI Insight. PMID 31999647.

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1. Bruner *et al.* A quantitative approach for measuring the reservoir of latent HIV-1 proviruses.
2. Procopio *et al.* A Novel Assay to Measure the Magnitude of the Inducible Viral Reservoir in HIV-infected individuals. EbioMedicine. 2015 Jun 27. PMID 26425694.