Reviewer’s report

Title: Impact of maternal HIV-1 viremia on lymphocyte subsets among HIV-exposed uninfected infants: Protective mechanism or immunodeficiency?

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Reviewer: ann chahroudi

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This manuscript by Kakkar et al provides a retrospective analysis of lymphocyte percentages early in life in HIV-exposed, uninfected infants and stratifies them by the level of maternal viremia near delivery. The authors found a statistically significant decrease in % of CD4+ T cells in 2 and 6 month olds whose mothers had higher viral loads (ie, >1000 compared to <50). The inverse was found to be true for % of CD19+ B cells (ie, greater percentage seen in infants born to moms with lower viral loads). These differences remained statistically significant after adjusting for gender, race, gestational age, and maternal / infant antiretroviral drug use. The authors conclude that in utero exposure to high levels of maternal HIV-1 may influence the developing immune system.

Major Points:

1. The differences found in CD4 and CD19 percentages between groups are relatively small and there is no evidence provided that these differences are clinically relevant. The methods section states that this cohort of HIV exposed uninfected patients were followed frequently in the first 2 years of life, then annually until age 5, and every 2 years thereafter. I wonder if the authors could provide clinical outcomes data for these patients – ie, were there increased infectious disease diagnoses / hospitalizations / mortality seen in infants born to mothers in the highest viral load group?

2. The lymphocyte subsets studied were very basic. Do the authors have further specimens available to look more closely at CD4+ and CD8+ T cell subsets (ie, naïve vs memory)? Was the HIV specificity of the CD4+ and CD8+ T cells ever assessed in this population? It would also be interesting to note whether the activation status of CD4+ and CD8+ T cells differed between the maternal viral load groups (immune activation might be predicted to be higher in infants born to mothers with higher viral loads).

3. The middle viral load group (ie, VL 50-1000) does not appear to be particularly informative. As the authors state, this may be related to viral loads reported to be < 500 (from the early time period of the cohort) that were actually < 50 (if a more sensitive assay had been available for use). Could the authors reanalyze this group using available true values (ie, discard all subjects with reported VL < 500)?

4. It would be helpful to know the range of viral loads in the > 1000 group.
5. In the abstract the authors state “These differences persisted until 6 months of age”. Were the lymphocyte percentages studied in these patients after 6 months of age? Were any differences seen?

6. There was a wide range of antiretroviral regimens provided to these infants to for PMTCT (from no ART to triple therapy). For how long were the ARV regimens used? Did the authors compare lymphocyte percentages at 2 months (either while on ART or soon after discontinuation) in the different ART groups? They did control for infant ART exposure in the adjusted analysis, but I wonder if there was an effect of individual regimens on the immune cells examined.

Minor Points:
1. Page 4, line 13 references listed are “18-120” – I think the authors meant “18-20”.

2. Page 10, line 20 please spell out “UU” (unexposed, uninfected)

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare I have no competing interests.