Metabolomic Perturbations of Tryptophan & Arginine Metabolites in the Breast Milk of Women With HIV

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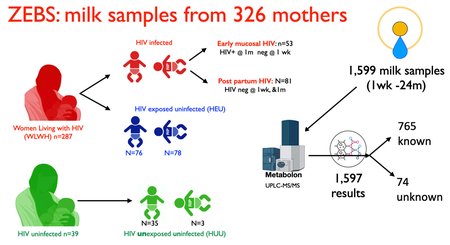
BACKGROUND

Children born to women with HIV (WWH), but not infected (HIV-exposed uninfected, CHEU) have two to three times the mortality rate of infants born to women without HIV (WWoH). Tryptophan is an essential amino acid critical for immune development, neurocognitive development, and growth. L-arginine is the substrate for production of nitric oxide (NO) and NO has a role in the control of infectious pathogens. We investigated the milk metabolome from WWH and WWoH in the pre-ART era to determine if metabolic perturbations may contribute to the impaired immune development of children born to WWH.

Tryptophan depletion in the milk of Women with HIV (WWH) may contribute to the impaired immune development of children who are HIV-exposed uninfected (CHEU).

METHODS



- Untargeted metabolomics was performed on 1599 breast milk samples from a RCT conducted in Zambia 2001-2008[1].
- The milks of WWH were separated by infant outcome into: CHEU who survived (n=76) or died (n=78) and infants who acquired HIV early (EMT, n=53) or through milk (PPT, n=81).
- Linear mixed effects models were used to identify differentially abundant compounds in breast milk between the infant outgroups among WWH and WWoH.
- All p-values were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate method.

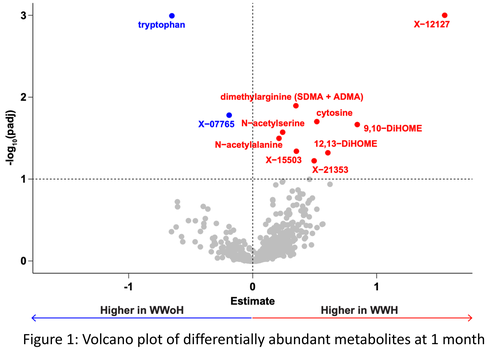


Figure 1: Volcano plot of differentially abundant metabolites at 1 month postpartum

RESULTS

- Differentially abundant metabolites are shown at 1 month postpartum (Fig 1).
- Tryptophan levels were significantly lower in the milk samples of WWH compared to WWoH at all timepoints from 1 week through 18 months. (Fig 2).

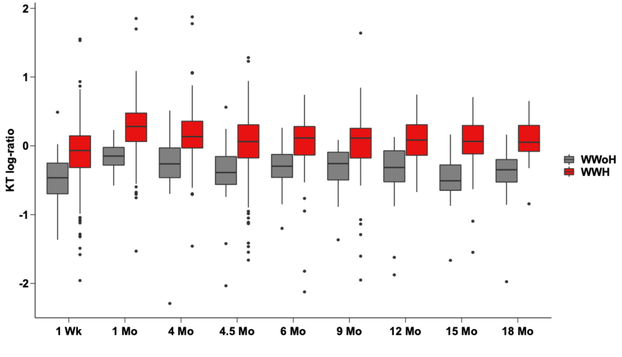


Figure 3: Kynurenine:tryptophan (KT) ratio is significantly higher in WWH

- Log-transformed kynurenine:tryptophan (KT) ratios were elevated in the milk of WWH at all timepoints ($p < 0.001$; Fig 3).
- Findings of lower tryptophan and elevated KT ratios in WWH were confirmed with Quantitative KT panel in 101 milks (KT ratio data shown Fig 4).

[1]Kuhn L et al. Effects of early, abrupt weaning on HIV-free survival in children in Zambia. NEJM 2008 359(2):130-41.

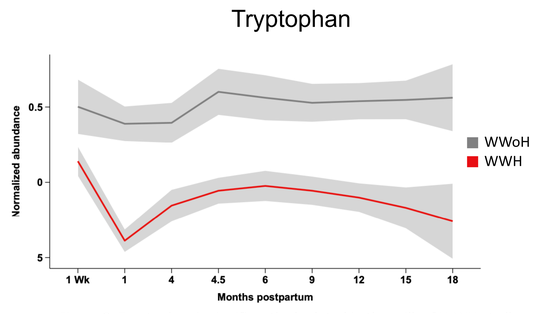


Figure 2: Tryptophan is significantly depleted in the milk of WWH at all timepoints.

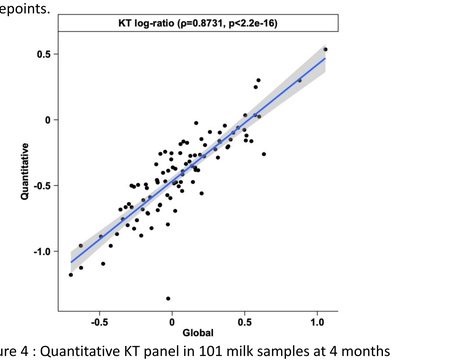
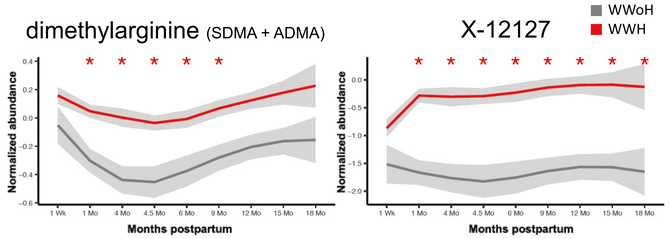


Figure 4 : Quantitative KT panel in 101 milk samples at 4 months confirms findings from global panel KT in all 1525 milks in final analysis

- The KT-ratio at 1 month was correlated with baseline maternal plasma and 1 month breast milk HIV RNA (r^2 of 0.28 and 0.20, respectively), and inversely with baseline CD4 count (r^2 = -0.32); all p<0.001.



- Dimethylarginine (symmetric+asymmetric (S+ADMA) was elevated in the milk of WWH during the first 9 months of lactation following the first week of life.
- A novel metabolite, X-12127, was significantly elevated in the milk of WWH at all timepoints following the first week of life ($p<0.001$ through 12 mos, then $p<0.1$ thereafter).

CONCLUSIONS

Tryptophan is significantly lower in the milk of WWH throughout early infancy. As breast milk is as the only source of this essential amino acid, this depletion may contribute to the immune, growth and neurodevelopmental abnormalities in children born to WWH. SDMA inhibits cellular update of L-arginine and ADMA competitively inhibits nitric oxide synthase leading to reduced NO bioavailability. Decrease NO may increase susceptibility to pathogens. Identifying key alterations and novel therapeutics is of critical importance for the 1.3 million children born to WWH each year.

FUTURE DIRECTIONS

- Future investigations will confirm findings in other cohorts with CHEU. Identification of X-12127. Role of tryptophan repletion in CHEU to improve clinical outcomes.

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