Expanded CD56$^+$ Subset in HIV-1$^+$ Mothers on HAART is Associated with Premature Delivery

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Introduction

In recent years progress and availability of HIV treatment and care, particularly HAART, has lead to a decline in AIDs diagnoses [1]. However the incidence of pregnant HIV infected UK-born women, although small (0.46 per 1000 women in 2009), has seen a gradual increase since 2000 [2]. The UK prevalence of recently acquired infections among new HIV diagnoses in heterosexual women of child bearing age (15-49 yrs) is 27% [1].

Recent evidence has shown that HIV-1 infected mothers experience a higher incidence of preterm delivery and low birth weight neonates with associated short and long term implications for the neonate [3]. This study aims to relate the composition of peripheral maternal lymphocyte subsets at delivery to the outcome of the pregnancy.

Methods

A retrospective review of 186 HIV-1$^+$ positive, pregnant women who delivered between 2002 and 2009 was undertaken. 31 women delivered preterm (defined as less than 37 weeks gestation) and 155 women delivered at term (T). Maternal demographics, gestation and lymphocyte subsets (CD3, CD4, CD8, CD19, and CD56), recorded longitudinally during pregnancy, were collected from a pre-existing database. Preterm delivery (PTD) was further classified as preterm spontaneous vaginal delivery (PTSVD) or preterm caesarean section (PTCS). Longitudinal modelling was performed with the aid of a statistician. Independent samples were analysed using the Mann-Whitney U test (Graphpad Prism 5.0). Statistical significance was defined as $p<0.05$.

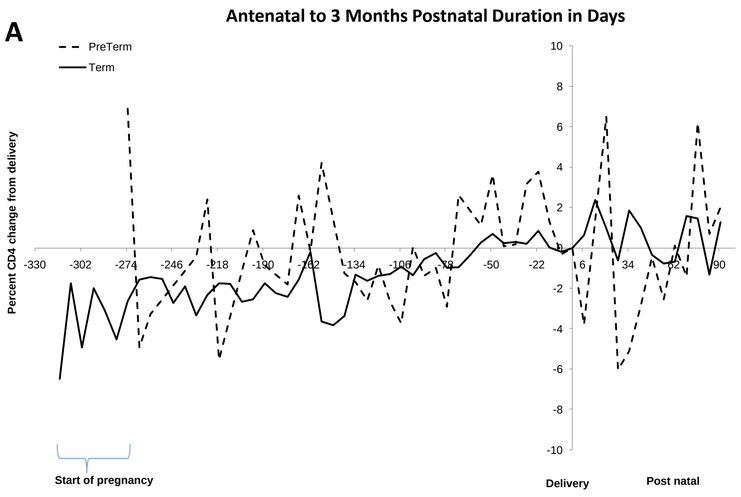
Results

Demographic, immunological and Virological Data

	Number of pregnancies = 186		
	Pre-term N=31	**Term N=155**	**^p-value**
Demographics			
Ethnicity (%) Caucasian / Black African / Other	6(19.4) / 16(51.6) / 9(29.0)	16(10.3) / 95(61.3) / 44(28.4)	0.334
#Mean age at pregnancy, years [range]	33.7(4.7) [22.5 to 39.8]	31.6(6.5) [18.2 to 49.7]	0.046
Median time since HIV-1$^+$ diagnosis to pregnancy, years (IQR) [range] *Negative values indicate HIV diagnosed during pregnancy*	4.2(1.4 to 6.3) [-0.5 to 14.5]	2.2(0.2 to 4.8) [-0.7 to 13.7]	0.096
Median nadir CD4$^+$ T-cell count, cells/µl blood (IQR) [range]	186(45 to 281) [2 to 730]	186(112 to 273) [2 to 733]	0.544
Median most recent CD8$^+$ T-cell count, cells/µl blood (IQR) [range]	825(660 to 946) [338 to 1720]	783(548 to 963) [158 to 2223]	0.537
Median nadir CD19$^+$ B-cell count, cells/µl blood (IQR) [range]	48(22 to 92) [10 to 205]	60(34 to 106) [2 to 274]	0.376
Median nadir CD56 natural killer cell count, cells/µl blood (IQR) [range]	24(12 to 45) [6 to 124]	21(13 to 40) [0.4 to 193]	0.590
Virology			
Median highest recorded HIV-1 load, RNA copies/ml plasma (IQR) [range]	59100(15443 to 174887)	20558(3309 to 87196)	0.065

 # p-value using unpaired t-test
^p-value using Mann-Whitney U test for quantitative data and chi-squared test with Yates' correction for qualitative data

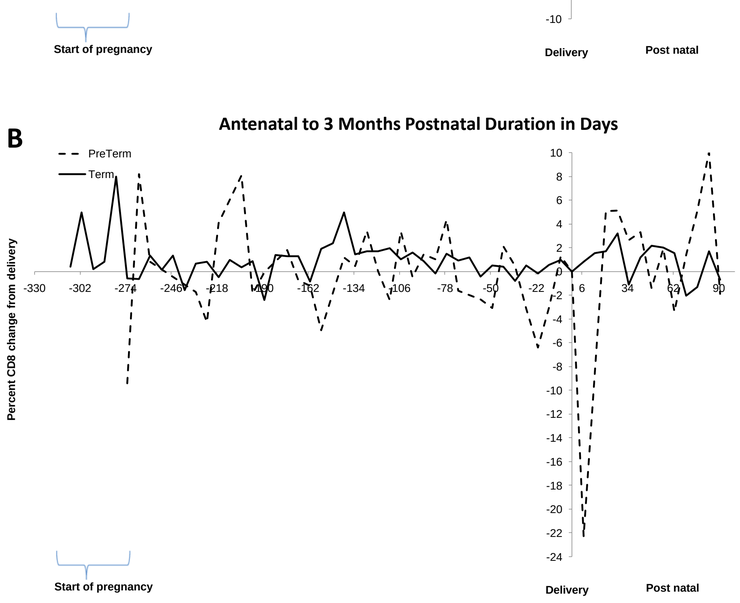
Longitudinal Analysis of Changes in Lymphocyte Subset Number/Proportion in Relation to Levels at Delivery



% CD4 T-cell count slope per 4 week intervals (95% CI):

Pre-delivery for PTD=0.4 (0.1 to 0.7), p=0.010; for T=0.4 (0.3 to 0.7), p=<0.001

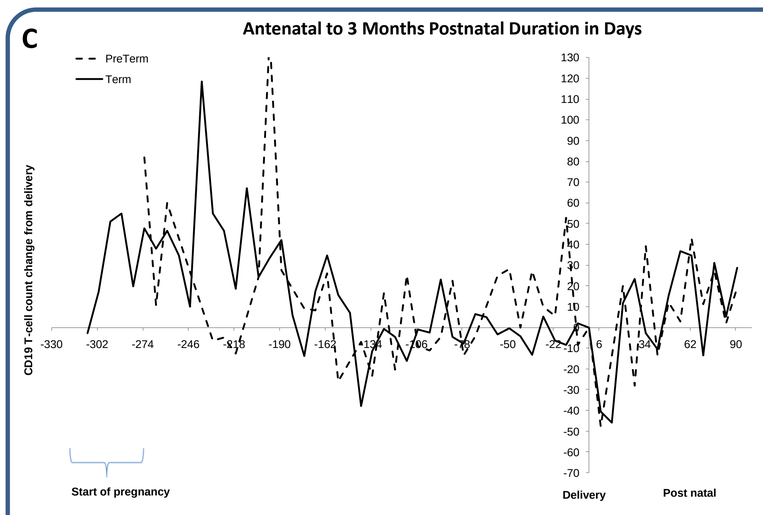
Postnatal slopes were not significant (ns)



% CD8 T-cell count slope per 4 week intervals (95% CI):

Pre-delivery for PTD=-0.5 (-1.0 to -0.1), p=0.026; for T=-0.2 (-0.3 to -0.1), p=<0.001

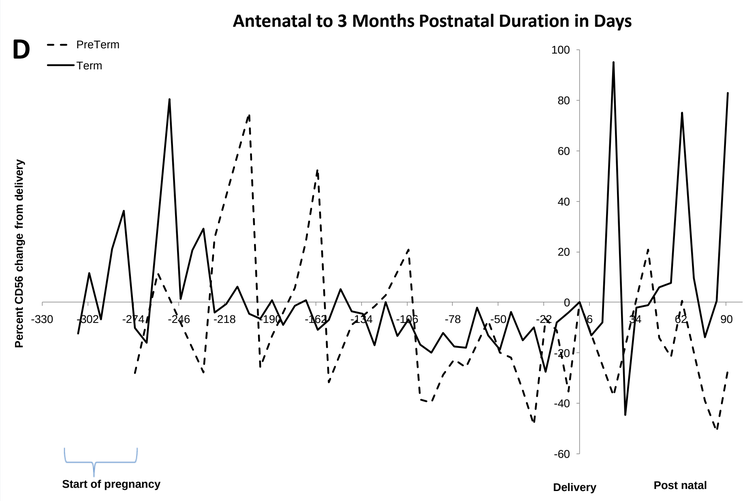
Postnatal for T=0.5 (0.0 to 0.9), p=0.031); slopes were ns for PTD



CD19 cell count slope per 4 week intervals (95% CI):

Pre-delivery for PTD ns; for T=-6.7 (-8.3 to -5.2), p=<0.001

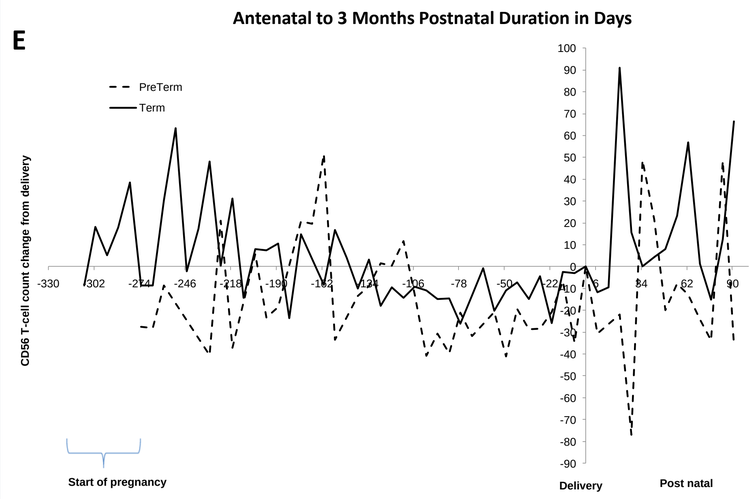
Postnatal for PTD ns; for T=14.0 (8.8 to 19.2), p=<0.001



% CD56 T-cell count slope per 4 week intervals (95% CI):

Pre-delivery for PTD -8.3 (-11.7 to -4.8), p=<0.001; for T=-4.5 (-5.8 to -3.3), p=<0.001

Postnatal for PTD ns; for T=13.8 (7.9 to 19.7), p=<0.001



CD56 T-cell count slope per 4 week intervals (95% CI):

Pre-delivery for PTD -5.5 (-8.4 to -2.6), p=<0.001; for T=-5.5 (-6.8 to -4.2), p=<0.001

Postnatal for PTD ns; for T=15.1 (9.5 to 20.8), p=<0.001

Figure 2. A and B) Both PTD and T are associated with increasing CD4 percentage during the antenatal period but decreasing CD8 percentage that returns to higher that delivery levels in T postnatal. C) T delivery is associated with decreasing CD19 percentage. D and E) Both PTD and T are associated with a decrease in CD56 percentage and count that increases postnatally in T but not in PTD.

Increased expression of CD56 is associated with preterm SVD

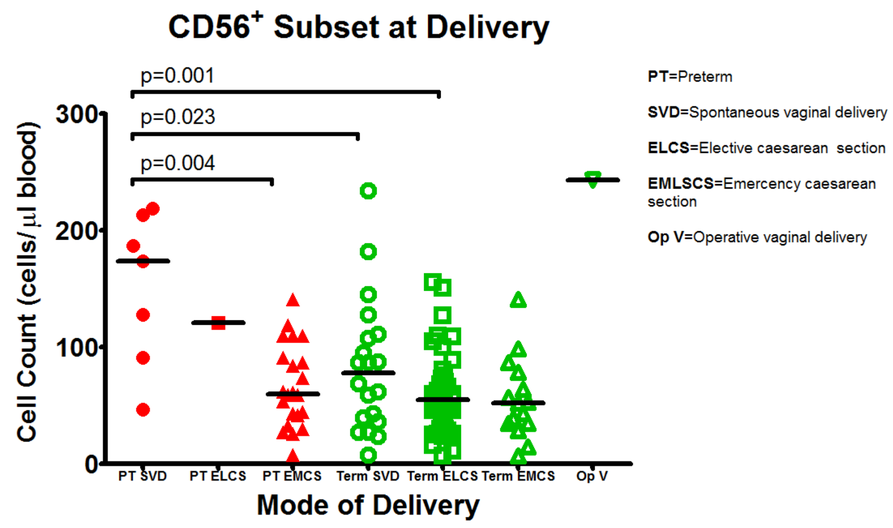


Figure 2. Comparing mode of delivery, PTSVD was associated with a greater number CD56$^+$ cells (median 174 cells/µl blood, IQR 91-213) than both term SVD (median 78 cells/µl blood, IQR 34-110; p=0.023) and term elective caesarean section (median 55 cells/µl blood, IQR 33-73; p=0.001) as well as PT EmCS (median 60 cells/µl blood, IQR 40-96; p=0.004). (Here PTD n=29, T n=83).

Conclusion

Total NK cell numbers are not thought to increase between healthy controls and HIV-1 infected patients but rather there may be a redistribution of NK cell subsets. Chronic viraemic HIV-1 infected individuals express greater proportions of pathologic NK subsets with altered expression of inhibitory receptors. Our results show NK cell count decreases longitudinally during pregnancy in both PTD and T but shows a statistically significant increase in T postnatally. Interestingly CD56 count is comparatively higher in PTD versus T at delivery. Perhaps pregnancy in HIV-1$^+$ ART treated women is associated with an altered NK phenotype and redistribution of subsets that reduces the risk of vertical transmission but concurrently increases the chance of premature delivery.

References

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