High rate of HIV superinfection after delivery: secondary analysis of the PEPI trial

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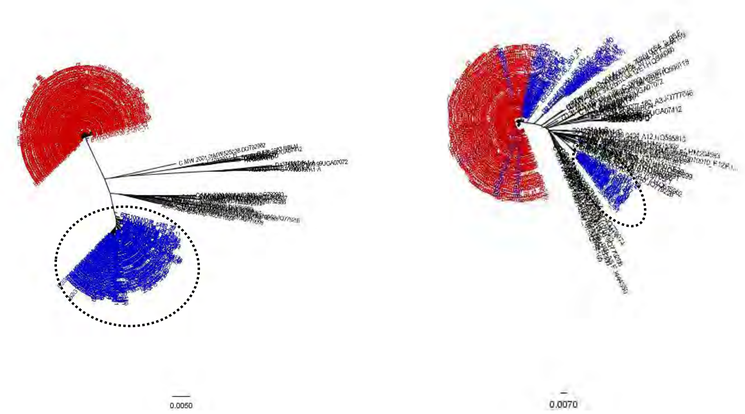
Background:

- HIV superinfection (SI) occurs when an HIV-infected individual is infected with a new, phylogenetically distinct HIV strain.
- Rates of HIV SI are higher in populations at increased risk of primary HIV infection, such as female sex-workers.
- HIV SI can cause temporary and sustained increases in viral load, which could increase the risk of HIV transmission to other individuals.
- Postpartum women are at increased risk of HIV infection, particularly at the time when sexual activity is resumed.
- It is not known if there is an increased risk of HIV SI in HIV-infected women postpartum or if maternal HIV SI increases the risk of MTCT of HIV during breastfeeding.

Methods:

- The Post-Exposure Prophylaxis of Infants trial in Malawi (PEPI-Malawi, 2004-2009) demonstrated that the risk of MTCT of HIV via breastfeeding was significantly reduced by providing infants an extended regimen of nevirapine or nevirapine plus zidovudine prophylaxis up to age 14 weeks, compared to infants who received a short regimen for prophylaxis (single dose nevirapine with one week of zidovudine).
- Samples from women who transmitted HIV to their infants via breast milk; (infants were negative for HIV at six weeks of age but positive later) were classified as transmitters and screened for HIV-SI (n=91).
- The 91 cases were matched as a group to women who did not transmit to their infants (non-transmitters) by study arm, follow-up time and sample availability.
- Samples from delivery and a follow-up visit for each woman were amplified and pyrosequenced in two genomic regions (p24 and gp41).
- HIV SI was established if the follow-up sample contained a new, phylogentically distinct population that was a greater genetic distance from the original viral strain than what would be expected based on evolution.
- Fisher's exact, Wilcoxon Rank Sum and Kruskal-Wallis tests were used.
- HIV SI and transmission risk was examined by multiple logistic regression.
- Rates of SI were calculated as incidence rate ratios (IRR)
- Risk factors for HIV SI were examined by logistic regression.

Figure 1: Non-transmitter Case #7-gag and gp41



p24 distance=2.3% **gp41 distance=6.6%**

Figure 1: HIV SI case in non-transmitter. Phylogenetic tree of consensus p24 and gp41 viral sequences (≥10 reads) derived from 454 pyrosequencing of a baseline (red) and follow-up sample from 2-years later (blue) with the superinfecting strain indicated (dashed circle). Samples are grouped with a selection of subtype reference and Malawian HIV sequences (black).

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Results:

- Non-transmitters had significantly higher CD4 cell counts (p=0.001), lower HIV viral loads (p<0.0001), and shorter breastfeeding duration than transmitters (p=0.048)
- Five cases of SI were identified among transmitters and five among the non-transmitters (p=1.0).
- Rate of SI in transmitters = 4.7/100py; 95% CI=1.5-11.0
- Rate of SI in non-transmitters = 4.4/100py; 95% CI=1.4-10.3
- Incidence rate ratio =1.1, 95% CI=0.3-4.7; p=0.92

Table 1. Logistic regression of SI and HIV transmission to infant

		Unadjusted		Adjusted	
Factors	**n/N**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Superinfection			**1.00**		**0.30**
No (ref)	**172/182**	**1**		**1**	
Yes	**10/182**	**1.00 (0.22-4.51)**		**2.32 (0.47-11.47)**	
Age			**0.44**		**0.53**
17-24 yrs (ref)	**68/182**	**1**		**1**	
≥25 yrs	**114/182**	**1.32 (0.70-2.53)**		**0.79 (0.37-1.66)**	
PEPI study arm			**1.00**		
Control (ref)	**56/182**	**1**			
Intervention	**126/182**	**1.00 (0.51-1.97)**			
Baseline CD4			**0.002**		**0.11**
<250 cells/ul (ref)	**49/172**	**1**		**1**	
≥250 cells/ul	**123/172**	**0.33 (0.15-0.69)**		**0.50 (0.22-1.16)**	
Baseline log10 VL			**0.001**		**0.004**
<4 copies (ref)	**55/157**	**1**		**1**	
≥4 copies	**102/157**	**3.44 (1.64-7.43)**		**3.06 (1.44-6.54)**	

- Maternal HIV SI did not significantly effect the odds of MTCT of HIV (adjOR=2.32, 95% CI=0.5-11.5).
- Longer breastfeeding duration was associated with a lower risk of HIV SI controlling for baseline viral load and PEPI study arm (adjOR=0.75; 95% CI=0.63-0.98).

Table 2. Logistic regression models of selected risk factors and SI

		Unadjusted		Adjusted	
Factors	**n/N**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age			**0.86**		**-**
17-24 yrs	**68/182**	**1**		**-**	
≥25 yrs	**114/182**	**0.89 (0.24-3.27)**		**-**	
Parity			**0.84**		**-**
1-2	**60/182**	**1**		**-**	
>2	**122/182**	**1.16 (0.29-4.64)**		**-**	
PEPI study arm			**0.19**		**0.45**
Control	**56/182**	**1**		**1**	
Intervention	**126/182**	**0.42 (0.12-1.52)**		**0.54 (0.11-2.71)**	
Baseline CD4, 100 cells/uL		**0.97 (0.69-1.34)**	**0.84**		
Baseline log10VL, copies		**0.46 (0.17-1.24)**	**0.12**	**0.40 (0.13-1.19)**	**0.10**
Time to resumption of sex, mos		**0.90 (0.73-1.11)**	**0.32**		
BF duration, mos		**0.78 (0.62-0.99)**	**0.04**	**0.75 (0.56-1.00)**	**0.05**

Conclusions:

- We observed a relatively high rate of HIV-SI in postnatal HIV-infected women.
- HIV SI did not increase the risk of postnatal MTCT in this cohort.
- Further research is needed to determine the relationship between HIV SI and transmission.

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