Pre-ART Vertical HIV Transmission Rates in Uganda Vary by Sex of Child and Maternal Viral Subtype

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BACKGROUND

- Across East Africa, HIV-1 subtypes A and D predominate
- Female infants are at a higher risk of perinatal transmission
- Among adults, the impact of subtype on transmission and mortality is clear:

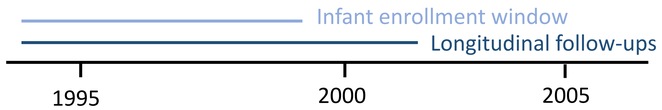
Subtype-specific impacts in *adult* HIV-1 transmission

Subtype A	Subtype D
↓ Less pathogenic	↑ More pathogenic
↑ More transmissible	↓ Less transmissible

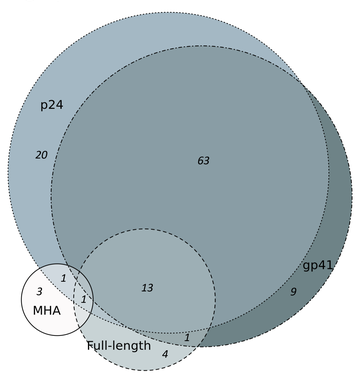
However, it is unknown whether these trends are the same in perinatal transmission. Current reports are conflicting, and there is no scientific consensus.

METHODS

To address this gap, we analyzed perinatal transmission risk by both infant sex and maternal subtype in a cohort of 131 mother-infant pairs in pre-ART Uganda.



We analyzed infant outcomes from the mothers living with HIV in the Mother Infant Supplementary Study, conducted in the late 1990s as part of the Rakai Community Cohort Study. Data was collected on infant HIV status, infant mortality, and various demographic characteristics.



We combined this epidemiologic data with subtyping data from a variety of sources, as shown in Figure 1. Only mother-child pairs with non-recombinant subtype A or D were included for further analysis.

Figure 1. Euler plot for the source of maternal subtype data. N = 115 mothers with subtype A or D.

Perinatal transmission was higher with maternal HIV-1 subtype A as compared to subtype D for female infants, but not males, in a pre-ART Ugandan cohort

RESULTS

Perinatal transmission by maternal subtype

Across the cohort, female infants were at a higher risk of perinatal transmission (RR=2.70, CI=1.19-6.13, p=0.02), as were infants born to mothers with subtype A (RR=2.96, CI=1.46-6.01, p=0.008)

Among male infants only, maternal subtype A led to no increased risk of perinatal transmission: RR = 0.99, CI: 0.12-6.83, p = 1).

However, female infants born to mothers with subtype A had a significantly increased risk of infection (RR = 3.54, CI=1.58-7.91, p=0.006).

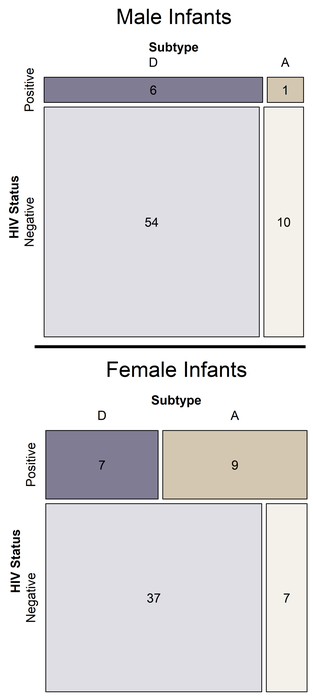


Figure 2. Mosaic plots of infant HIV status by maternal subtype.

Infant mortality by maternal subtype

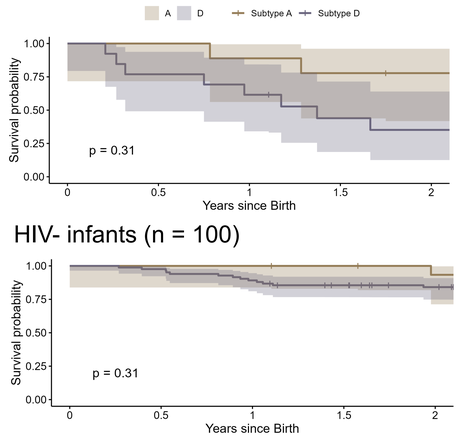


Figure 4. Kaplan-meier plots of infant survival, striated by maternal subtype.

The two-year survival for infants with subtype A was 77.8% [CI: 41.8%-96.1%] while for subtype D it was only 35.1% [CI: 12.5%-64.0%], though this was not significantly different (Figure 4). This trend also held among HIV- children of HIV+ mothers.

Impact of viral load on perinatal transmission

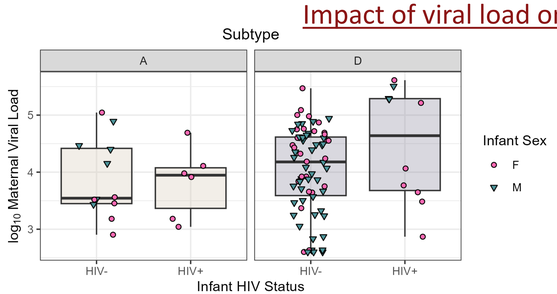


Figure 3. Boxplots showing the maternal viral loads striated by maternal subtype and infant HIV status.

To account for the known positive association between viral load and transmission risk, we compared maternal viral loads across infant HIV status, infant sex, and maternal subtype for the 98 mother-infant pairs with known viral loads (Figure 3). There were no significant differences between categories, and the median viral load for mothers with subtype D was higher than that for mothers with subtype A.

CONCLUSIONS

Across our cohort of ART-naïve Ugandan children exposed to HIV-1 subtype A or D:

- Female infants were at a significantly higher risk of perinatal HIV acquisition than male infants
- Infants born to mothers with subtype A were at a significantly higher risk than those born to mothers with subtype D
- This subtype-specific risk was not evenly distributed:
  - Among male infants only, there was no increased risk associated with maternal subtype
  - Among female infants, there was a 3.5-fold increase in perinatal acquisition risk with maternal subtype A
- These findings are not solely attributable to differences in maternal viral load between subtype A and D, or between mothers pregnant with male and female infants
- Although there was no significant difference in the mortality of infants born with subtype A or D, infants with subtype D had a two-year survival rate of less than half when compared to infants with subtype A
- Our lack of significant findings here likely represents a lack of power for the mortality analysis specifically

These findings could provide insight into the mechanisms governing perinatal transmission. Additionally, they highlight the importance of disaggregating transmission data by sex.

ACKNOWLEDGEMENTS + CONTACT

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PLAIN LANGUAGE SUMMARY: In East Africa, there are two main subtypes of HIV: subtype A and subtype D. We still do not know which subtype is more likely to be passed from a mother to their child. Here, we showed that subtype A is more transmissible, but specifically, that this difference is seen in female infants but not males.