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BRIEF REPORT

Pre–Antiretroviral Therapy Vertical HIV-1 Transmission Risk in Uganda Varies by Sex of Child and Maternal Viral Subtype

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We analyzed perinatal transmission in a pre–antiretroviral therapy Ugandan cohort by maternal human immunodeficiency virus type 1 subtype and infant sex in 131 mother-child pairs. Among all children, if the mother was infected with subtype A there was a nearly 3-fold increased risk of perinatal transmission compared with subtype D (risk ratio [RR], 2.96 [95% confidence interval (CI), 1.46–6.01]; $P = .008$). When stratifying infants by both sex and maternal subtype, significantly more female (56.3% [9 of 16]) than male (9.1% [1 of 11]) infants born to mothers with subtype A were infected (RR, 6.19 [95% CI, .91–42.12]; $P = .02$). In contrast, among infants born to mothers with subtype D, transmission rates were comparable across sex (RR, 1.59 [95% CI, .57–4.41]; $P = .39$).

Analyzing perinatal transmission in a pre–antiretroviral therapy Ugandan cohort by maternal human immunodeficiency virus type 1 subtype and infant sex, we found that subtype A was more vertically transmissible than subtype D, but only in female infants.

Keywords. perinatal transmission; sex; subtype; maternal; vertical transmission.

Over the past 2 decades, advances in antiretroviral therapy (ART) have dramatically reduced rates of vertical human immunodeficiency virus (HIV) type 1 (HIV-1) transmission. Without treatment, the risk of transmission during pregnancy or delivery can reach as high as 29%. When maternal viral suppression is sustained, the risk falls below 0.5%; but these gains are contingent on uninterrupted access to treatment [1]. As a result, perinatal transmission remains a major challenge in regions where ART coverage remains inconsistent. In 2024, there were an estimated 120 000 new pediatric HIV infections globally, with 86% of cases occurring in Africa, particularly in regions with limited ART access [2].

In East Africa, where HIV subtypes A and D predominate, data suggest that subtype can affect adult heterosexual transmission and pathogenesis. In the absence of ART, subtype D is associated with faster disease progression and higher mortality rates [3], while subtype A appears to be more transmissible, even with adjustment for viral load (VL) [4]. However, far less is known about the role of subtype in perinatal transmission and infant mortality. In Tanzania, some cohorts report higher perinatal transmission of subtype A than of subtype D [5], whereas studies from Kenya suggest greater transmission of subtype D [6] or no subtype-specific differences [7]. The impact of subtype on mortality rates in infants is still unclear [8].

Infant sex has been identified as a key modifier of perinatal transmission risk. Across geographic regions and viral subtypes, transmission is consistently higher among female infants [9]. Although this trend is not fully understood, sex-based differences in inflammation have been proposed as a possible contributing factor [9]. Moreover, the potential interaction between subtype and infant sex has been underexplored. To address this gap, we performed a retrospective analysis of perinatal transmission and infant survival in pre-ART Uganda. We estimated the impact of both sex and subtype on perinatal transmission and calculated subtype-specific mortality rates.

METHODS

Study Cohort

To compare the effects of subtype and sex on transmission, we evaluated HIV acquisition and survival outcomes for infants born to mothers with HIV in Uganda between 1995 and 1999, before ART became available. All participants were part of the Mother Infant Supplementary Study (MISS), a cohort of pregnant women enrolled from the Rakai Community Cohort Study [10, 11]. All mothers provided written, informed consent. The HIV status of the children was determined using polymerase chain reaction during the first 6 weeks of life. Mother-child pairs were selected from the original MISS if the mothers were known to be infected with HIV subtype A or D and if the sex and HIV status of the child was known.

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Available maternal VL data were also included in the analysis but was not a requirement for this study. No participants received ART during this study. Data on the subtype of maternal infections were pooled from previous studies, with subtyping methods including p24 and gp41 fragment sequencing, long-read sequencing, and multiregion hybridization, as described in the Supplementary materials.

Statistical Analyses

We assessed the association between transmission and both sex and subtype using risk ratios (RRs) and Fisher exact tests for statistical significance. To investigate the established positive correlation between VL and transmission risk [12], we compared log-transformed maternal VLs across infant sex, maternal subtype, and infant HIV status using *t* tests, and we computed the adjusted RRs from a multivariate binomial log-link model on infant sex, maternal subtype, and maternal VL. We compared differences in mortality rates before age 2 years across subtype for both HIV-positive and HIV-negative children using Cox proportional hazards and Kaplan-Meier analysis with confidence intervals (CIs) calculated using the beta product confidence procedure. For all analyses, statistical significance was defined as a 2-tailed α value of .05%, and 95% CIs were calculated. All analyses were performed using R software (version 4.5.2).

RESULTS

Cohort Descriptions

The MISS enrolled 667 mother-child pairs, of which 327 (49.0%) had data on maternal subtype available. Of those 327, 150 (45.9%) had data on the infant HIV-1 status available. Of those 150 pairs, 27 infants (18.0%) were born to mothers with subtype A and 104 (69.3%) to mothers with subtype D. All children born to mothers with recombinant subtypes (12.7% [19 of 150]) were excluded from analysis due to the heterogeneity of possible recombinant subtypes. For the remaining 131 children, HIV status was determined between birth and 6 weeks after birth, primarily at birth (n = 75 [57.3%]) or 4–6 weeks after birth (n = 62 [47.3%]). For the 44 infants (33.6%) tested more than once, the last test available was used. Most mothers had VL data available: 18 of 27 with subtype A (67%) and 80 of 104 with subtype D (76.9%). Nine infants (6.9%) were lost to follow-up, and of the remaining 122, outcomes were tracked for a median of 3.23 years (interquartile ratio [IQR], 1.61–4.54 years).

Transmission

Regardless of the HIV subtype they were exposed to, female infants had a higher risk of infection than male infants (RR, 2.70 [95% CI, 1.19–6.13]; $P = .02$). Among all children, if the mother was infected with subtype A there was a nearly 3-fold increased risk of perinatal transmission, compared with subtype D (subtype A vs D, 10 of 27 [37.0%] vs 13 of 104, [12.5%]; RR, 2.96 [95% CI, 1.46–6.01]; $P = .008$). When infants were stratified by both sex and maternal subtype, significantly more female (56.3% [9 of 16]) than male (9.1% [1 of 11]) infants born to mothers with subtype A were infected (RR, 6.19 [95% CI, .91–42.12]; $P = .02$). In contrast, among infants born to mothers with subtype D, transmission rates were more comparable across sex: 15.9% (7 of 44) in female versus 10.0% (6 of 60) in male infants (RR, 1.59 [95% CI, .57–4.41]; $P = .39$) (Figure 1). Notably, female infants born to mothers with subtype A had a 3.54-fold increased risk of infection (56.3% [9 of 16]) compared with those born to mothers with subtype D (15.9% [7 of 44]) (RR, 3.54 [95% CI, 1.58–7.91]; $P = .006$). This was not observed in male infants (RR, 0.99 [95% CI, .12–6.83]; $P > .99$).

VL and Transmission

There were no significant differences between the VLs of mothers by subtype, infant sex, or transmission status, though the majority of infants (5 of 9 [55.6%]) whose mothers had high VLs ($\log_{10} > 5.0$) became infected, compared with only 9.1% (1 of 11) of those with low VLs ($\log_{10} < 3.0$). Mothers of infants who contracted HIV perinatally had a median $\log_{10}$ VL of 4.02 (IQR, 3.61–5.23), whereas those whose infants did not become infected had a median $\log_{10}$ VL of 4.12 (3.51–4.61; $P = .38$). Mothers with subtype A had a median VL of 3.74 (IQR, 3.44–4.34) and those with subtype D had a median VL of 4.18 (3.62–4.67; $P = .20$). Mothers of female and male infants had similar VLs (mothers of female infants, 4.09 [IQR, 3.58–4.69]; mothers of male infants, 4.08 [3.46–4.60]; $P = .47$) (Supplementary Figure 1). In a multivariate model of infant acquisition risk by maternal subtype, maternal VL, and infant sex, female sex was associated with a 4.14-fold higher risk of acquisition (95% CI, 1.26–13.7; $P = .02$), and maternal subtype A was associated with a 2.39-fold higher risk of transmission (95% CI, 1.02–5.61; $P = .045$).

Mortality Rates

There was no significant difference in the risk of death before age 2 years by maternal subtype, although only 35.2% (95% CI, 16.2%–76.1%) of children with subtype D survived to age 2 years, compared with 77.8% (54.9%–100%) of those with subtype A (hazard ratio, 2.25 [95% CI, .47–10.80]; $P = .31$) (Figure 2*A*). This same pattern held among children without HIV born to HIV-positive mothers (hazard ratio, 2.90 [95% CI, .38–22.16]; $P = .31$) (Figure 2*B*).

DISCUSSION

In this retrospective analysis of pre-ART perinatal HIV transmission in Uganda, we found that subtype A was more transmissible than subtype D. Notably, this difference in

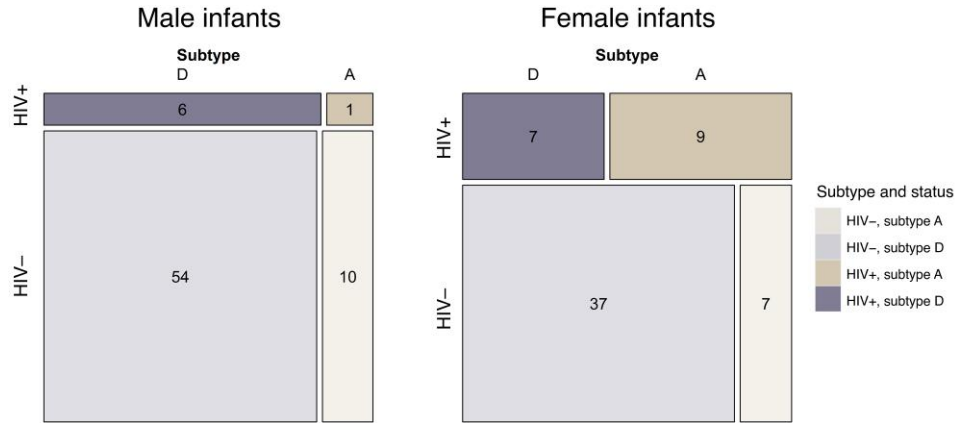

Figure 1. Perinatal transmission by infant sex and maternal subtype. Mosaic plots separated by infant sex, showing human immunodeficiency virus (HIV) 1 status by the mother's subtype. Numbers on the plots and box sizes represent the number of infants in each category. Abbreviations: HIV–, HIV negative; HIV+, HIV positive.

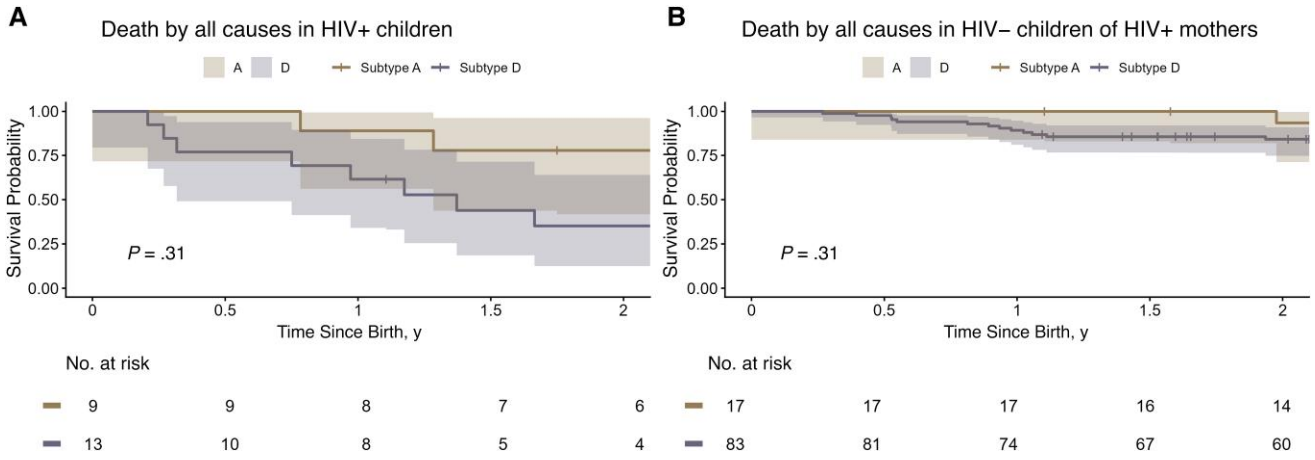

Figure 2. Survival outcomes of infants born to human immunodeficiency virus (HIV)–positive mothers, with Kaplan-Meier survival curves striated by maternal subtype. *A,* HIV-positive (HIV+) children infected perinatally. *B,* HIV-negative children (HIV−) born to HIV+ mothers. *P* values represent Cox proportional hazards for survival to 2 years of age. Number at risk indicates the number of participants being analyzed at a given time point.

transmission was primarily observed among female infants, who had a >6-fold increased risk of infection compared with male infants born to mothers with subtype A. The impacts of both sex and subtype on transmission risk remained significant even after adjustment for maternal VL.

In general, our results align with previously reported trends in perinatal transmission. As in previous cohorts, female infants were more likely to be perinatally infected than male infants, regardless of subtype. Although the mechanisms of this increased risk are not fully understood, it has been consistently observed [9]. Our finding that HIV-1 subtype A was more vertically transmissible than subtype D contributes to the conflicting literature on the impact of subtype on perinatal transmission. While some studies have reported higher perinatal transmission of subtype A than of subtype D [5], others have found no significant difference or found that D was more transmissible than A [6, 7]. Our findings align with the higher rate of HIV adult heterosexual transmission of subtype A relative to subtype D [4]. This could guide perinatal treatment and prevention efforts toward communities with higher rates of subtype A; however, these findings may not apply to communities with access to ART.

One possible explanation for why female infants born to mothers with HIV subtype A are more likely to be infected than those born to mothers with subtype D could be interferon (IFN) α resistance. IFN-α is an innate antiviral cytokine that disrupts viral replication. It has been linked to reduced HIV transmission, but the degree of protection hinges on viral susceptibility [13]. One study showed that IFN-α susceptibility differs by viral subtype, with recombinant AD transmitted founder viruses being more likely to be IFN-α resistant than subtype D transmitted founder viruses, suggesting that the

incorporation of subtype A genetic material could increase IFN-α resistance [14]. This is particularly relevant for sex differences in transmission, as females have generally higher levels of IFN-α, and recent evidence has shown that perinatally infected females are more likely to harbor IFN-α–resistant viruses, suggesting that higher levels of IFN-α in females select even more strongly for IFN-α–resistant viruses [13, 15]. These complex dynamics between infant sex, subtype, and transmission risk could be mediated by IFN-α, which could be why subtype A is more transmissible, specifically for female infants. Although this does not explain the baseline higher levels of transmission to female infants, it could be a mechanistic explanation as to why sex-specific risk appears to differ by subtype. Further research is needed to understand these trends.

We observed no significant differences in the risk of death for infants born with subtype A and those born with subtype D, although only 35.2% of infants with subtype D survived to 2 years of age, versus 77.8% of infants with subtype A. We were limited by sample size, as our cohort of children living with HIV consisted of only 25 individuals. In addition, we were unable to assess the effect of maternal death on infant survival, and the loss of maternal care may have adversely influenced infant outcomes. As subtype D is associated with faster disease progression in adults, it is likely that infants perinatally infected with subtype D are also more likely to experience maternal loss [3]. More research is necessary to determine the impact of maternal subtype on infant survival.

Our relatively small cohort also restricted our statistical power in assessing the interactions between infant sex and viral subtype. In addition, as many subtype assignments were generated with only fragment sequencing or molecular probe analysis, some recombinant strains may have been identified as nonrecombinant A or D. In future studies, we aim to update sequencing techniques to better identify the key motifs involved and how recombinant strains impact transmission. Finally, because HIV status was confirmed within the first 6 weeks of life, we were unable to distinguish between transmission in utero, during delivery, or through breastfeeding. Therefore, it is possible that our observations only reflect trends in certain routes of transmission. These constraints underscore the need for further research into the subtype-specific impacts on transmission.

Our findings contribute to the sparse literature on the role of subtypes on perinatal transmission of HIV in the absence of ART and could help guide perinatal transmission reduction efforts in regions with limited ART access. Consistent with trends observed in horizontal transmission, we found that subtype A was more vertically transmissible than subtype D. When assessing the interaction between sex and subtype, we found that female infants with subtype A were at the greatest risk of infection. This interaction may resolve previously conflicting findings on the relative vertical transmissibility of subtypes A and D, underscores the importance of considering infant sex when interpreting vertical transmission data and opens up several avenues for further research to establish the mechanisms governing acquisition.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Data availability. Data are available from the corresponding author upon reasonable request.

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