Could This Be Cell-Associated Perinatal HIV Transmission?

1219

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BACKGROUND

No HIV vertical transmissions in the French Perinatal Cohort among 5482 pregnancies fulfilling the following criteria [1]:

- Effective anti-retroviral therapy (ART) from conception
- Undetectable plasma HIV viral load (VL) near delivery*
- Infant post-exposure prophylaxis (PEP)
- No breast/chestfeeding.

**VL taken nearest to delivery (90 days before - 7 days after)*

Among pregnancies of people living with HIV in the UK diagnosed by the point of delivery, 60 vertical transmissions were reported 2006-2019 [2]. Of these, two cases fulfilling all 4 criteria above were referred to Imperial College Healthcare NHS Trust (ICHNT).

In the context of sustained undetectable plasma HIV are these transmissions due to perinatal transmission of lymphocytes with integrated HIV provirus (cell-associated transmission)? Cell-associated transmission is seen in *in vitro* and *in vivo* animal models of HIV [3,4], and is the primary form of transmission of human T-lymphotropic viruses [5].

Bi-directional cell transmission occurs during pregnancy [6]. Birthing parent cells embed in foetal tissues from 2nd trimester [7], are found in ~40% of cord blood samples [8] and maternal microchimerism persists into adulthood [9].

Without understanding whether this microchimerism may occur from cells with integrated retroviral DNA, we may not be able to fully eliminate vertical transmission of HIV.

METHODS

Case series and literature review of vertically-acquired HIV despite undetectable birthing parent HIV RNA. Infant/birthing parent viruses linked by HIV sequencing and phylogenetic analyses.

Case series of infants referred to ICHNT with vertically-acquired HIV in the absence of known risk factors for vertical HIV transmission, with infant and maternal clinical notes reviewed.

Literature review for cases of vertical acquisition of HIV in the presence of maternal virological suppression, and absence of other known risk factors. One case was seen in the DOLPHIN-2 study [10], with clear documentation of sustained suppression of postpartum maternal plasma HIV viral load.

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Translocation of birthing parent cells may occur *in utero* or during breast/chestfeeding

We present three cases of HIV vertical transmission in the absence of detectable plasma HIV RNA.

Were these transmissions driven by maternal microchimerism?

RESULTS

Case series. Maternal/infant viruses linked by HIV sequencing and phylogenetic analyses.

Case	ART	VL during pregnancy	Additional factors during pregnancy?	Gestation	Mode of delivery?	Infant PEP	Infant feeding	Infant VL at birth	Infant VL at 6 weeks	Infant VL at 12 weeks
A	ART pre-conception and throughout pregnancy. ART: Tenofovir-DF, emtricitabine, efavirenz Excellent adherence reported.	At 8 weeks GA VL 380 cpm. Subsequently VL measured x6 during pregnancy and at delivery, with all VL <50 cpm	Enoxaparin for 6 weeks from 11 weeks GA; Pre-eclampsia at 38 weeks GA	38 weeks	Vaginal delivery with induction of labour <1 hour rupture of membranes	Zidovudine PEP for 2 weeks*	Exclusive formula feeding	Not detected	Not detected	17.6 x 10^6 cpm
B	ART pre-conception and throughout pregnancy. ART: Tenofovir-DF, emtricitabine, ritonavir-boosted atazanavir Excellent adherence reported.	VL measured x5 during pregnancy and at delivery. All VL <50 cpm	Iron infusion at 33 weeks GA	36 weeks	Pre-labour pre-rupture of membranes Caesarian section	Zidovudine PEP for 4 weeks*	Exclusive formula feeding	Not detected	1.4 x 10^6 cpm	

*As per contemporaneous guidelines

Abbreviations: *ART anti-retroviral therapy; cpm copies per millilitre; GA gestational age; PEP post-exposure prophylaxis; VL viral load*

Literature review.

Dolphin-2: one late transmission with HIV sequencing linking infant and maternal viruses [10].

- Efavirenz-based ART commenced week 28 GA.
- Maternal HIV VL undetectable at delivery and post-partum at weeks 6, 12, 24, 48 and 72
- Maternal breastfeeding for 48 weeks: 24 weeks exclusively then 24 weeks mixed feeding.
- Infant HIV RNA testing negative at birth and weeks 6 and 12.
- HIV RNA first detected in infant at week 72.
- Stored maternal plasma at weeks 24 and 48 – HIV RNA negative.
- Breastmilk HIV RNA negative. No mastitis reported.

DISCUSSION

Case A: Pre-eclampsia can disrupt the maternal-foetal interface (Figure 1) and enhance cellular translocation [11]. Enoxaparin *in vitro* may reduce HIV virion production [12].

Case B: Intravenous iron may have reactivated latent HIV-containing cells to produce free virions [13], while the effects of iron on placental cell translocation are unknown.

DOLPHIN-2 case: Maternal microchimerism can occur via the infant gut. Introducing non-milk food sources is associated with infant gut inflammation and increased risk of postnatal HIV transmission in infants, particularly those <6months [14].

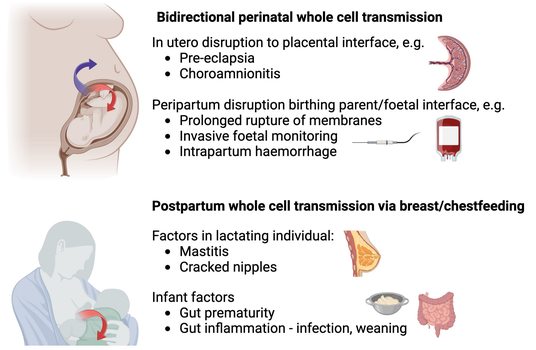


Figure 1: Factors associated with cell transmission to the foetus/infant

CONCLUSION

Development of maternal microchimerism from cells with integrated HIV may explain residual vertical transmission. This may be enhanced by factors encouraging the movement of cells to the foetus/infant (Figure 1), or reduced by factors affecting the ability of the foetus/infant to eliminate/prevent reactivation of maternally-derived cells, as seen in cases of infant immune dysfunction [15].

Cell-associated HIV transmission and persistence of HIV-containing cells in the foetus/infant may be reduced by exposure to ART. Birthing parent ART may act as foetal HIV pre-exposure prophylaxis (PrEP) *in* utero, though variable ART excretion into milk may limit its use as infant PrEP during breast/chestfeeding. Infant PEP provides postnatal cover for the duration of use.

With suppressed birthing parent plasma HIV VL, vertical transmission is rare but present. Improved understanding of cell-associated HIV transmission is necessary to eliminate vertical transmission.

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