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Duration of ruptured membranes and mother-to-child HIV transmission: a prospective population-based surveillance study

Running title : Rupture of membranes and mother-to-child HIV transmission

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Abstract

Objectives

To investigate the association between duration of rupture of membranes (ROM) and mother-to-child HIV transmission (MTCT) rates in the era of combination antiretroviral therapy (cART).

Design

The National Study of HIV in Pregnancy and Childhood (NSHPC) undertakes comprehensive population-based surveillance of HIV in pregnant women and children.

Setting

UK and Ireland.

Population or Sample

2398 singleton pregnancies delivered vaginally or by emergency caesarean section in women on cART in pregnancy in 2007-2012 with information on duration of ROM; HIV infection status was available for 1898 infants.

Methods

Descriptive analysis of NSHPC data.

Main Outcome Measures

MTCT rates.

Results

In 2116 pregnancies delivered at term, median duration of ROM was 3 hours 30 minutes (IQR: 1hr, 8hr). The overall MTCT rate for women delivering at term with duration of ROM ≥4 hours was 0.64% compared with 0.34% for ROM <4 hours, with no significant difference between the groups (OR: 1.90; 95% CI: 0.45, 7.97). In women delivering at term with viral load <50 copies/ml, there was no evidence of a difference in MTCT rates with duration of ROM ≥4 hours compared with <4 hours (0.14% for ≥4 hours versus 0.12% for <4 hour; OR: 1.14 (95% CI: 0.07, 18.27)). Among infants born preterm with infection status available, there were no transmissions in 163 deliveries where maternal viral load was ≤50 copies/ml.

Conclusions

No association was found between duration of ROM and MTCT in women taking cART.

Keywords

HIV, duration of ruptured membranes, mother-to-child transmission, pregnancy

Twitter abstract

Prolonged rupture of membranes is not associated with MTCT of HIV in women on effective ART delivering at term

Introduction

Mother-to-child HIV transmission (MTCT) rates in Europe are now very low, and reached 0.57% among diagnosed women in the United Kingdom and Ireland in 2007-2011.[1] In the era before combination antiretroviral therapy (cART) became widely available, elective caesarean section was shown to reduce the risk of MTCT compared with vaginal delivery.[2,3] However, the success of cART in treating HIV has meant that, in the absence of obstetric contraindications, women with suppressed virus at delivery can now normally expect to have a vaginal delivery.[4]

In the pre-cART era, several studies in untreated women or women receiving monotherapy indicated that prolonged rupture of membranes (ROM) was significantly associated with an increased risk of MTCT,[5,6] while others suggested no association.[7–9] A meta-analysis of 15 cohort studies suggested a 2% increase in relative risk of transmission per hour of ROM, where duration of ROM was less than 24 hours, but viral load was not considered.[10] Evidence from the cART era is sparse: a small study in Spain found an increase in transmission rates in untreated but not in treated women with duration of ROM greater than 6 hours (compared with less than 6 hours),[11] while a single-centre study in Miami found an association between MTCT and duration of ROM only where maternal viral load was greater than 1000 copies/ml.[12]

For women with spontaneous ROM after 34 weeks gestation, current British guidelines recommend immediate induction of labour if maternal viral load is <50 copies/ml, consideration of immediate caesarean section if maternal viral load is 50-999 copies/ml, and immediate caesarean section if viral load is greater than 1000 copies/ml.[4] Owing to the absence of data for ROM in preterm deliveries at less than 34 weeks gestation, management is recommended on a case by case basis. There is currently no guidance relating to duration of ROM in women who are in active labour at term, also due to a lack of evidence. The aim of this analysis was to investigate the association between duration of ROM and MTCT rates in women on cART delivering in the UK and Ireland between 2007 and 2012.

Methods

Comprehensive population-based data on HIV in pregnant women and children in the UK and Ireland are collected through the National Study of HIV in Pregnancy and Childhood, ongoing since 1990. Pregnancy and delivery data are provided by obstetric respondents, and information on duration of ROM has been collected since 2007. Infection status for all HIV-exposed infants is sought from paediatric respondents. Full details of methods are described elsewhere.[1,13]

Mode of delivery was classified as elective caesarean section (pre-labour, pre-rupture of membranes), emergency caesarean section (after rupture of membranes and/or onset of labour, or

for other emergency obstetric indications), or vaginal delivery (reported by obstetric respondents as planned or unplanned). Duration of rupture of membranes is defined as the time between rupturing of the amniotic sac and delivery of the infant; due to limitations of data collection we were unable to further differentiate whether ROM occurred before or after the onset of labour, and whether this occurred spontaneously or was iatrogenic Maternal HIV viral load closest to delivery (during pregnancy or up to seven days postpartum) was selected and categorised as <50 (undetectable), 50-399, 400-999, 1000-9999, and ≥10,000 copies/ml. Maternal CD4 cell count closest to delivery was classified as <200, 200-349, 350-499 and ≥500 cells/mm^3. Gestation <37 weeks was classified as preterm, and <34 weeks as early preterm.

Likely timing of infant infection was defined as: *in utero* where a positive HIV PCR was obtained within three days of birth; *in utero*/*intrapartum* where no PCR was reported within three days of birth, and a positive PCR between 3 days and 6 weeks of birth; *intrapatrum* where there was a negative PCR within 3 days of birth and positive PCR within 6 weeks; *intrapartum/postnatal* where there was a negative PCR at within 3 days of birth but no positive PCR until after 6 weeks; and *postnatal* where there was a negative PCR between 4 days and 6 weeks and positive thereafter. Transmissions where testing did not fall into these groups were classified as unknown.

Eligible pregnancies were all those reported by March 2013 in women diagnosed with HIV before delivery and on a combination of three or more antiretroviral drugs (cART) during pregnancy, who delivered singleton live-born infants between 1 January 2007 and 31 December 2012 in the UK and Ireland. Analyses were restricted to pregnancies where membranes were reported to have ruptured before delivery and duration of ROM was provided, and therefore all elective caesarean sections were excluded.

Statistical Methods

Data were managed in Access 2010 (Microsoft Corp., Redmond, Washington, USA), compiled using R version 2.14.2[14] and analysed using Stata version 12.1 (Stata Corp. LP, College Station, Texas, USA). Duration of ROM was classified as <4 hours, 4 to <24 hours, and ≥24 hours for descriptive purposes; MTCT rates in pregnancies with ROM <4 hours were compared with those with ROM ≥4 hours to facilitate comparison with other studies[4,8,9,12]. The low number of infected children, together with small numbers in certain groups, meant that multivariable analyses were not possible.

Results

Between 2007 and 2012 there were 7321 eligible pregnancies resulting in singleton live births to women diagnosed with HIV before or during pregnancy and on cART. We excluded pregnancies

delivered by elective caesarean section (2709/7321), missing mode of delivery (57/7321), births reported before ROM data were sought (131/7321) and deliveries by emergency caesarean where membranes were reported as ruptured only at delivery (616/7321). Duration of ROM was not stated for a further 19% (1410/7321) of the eligible pregnancies. The study population for analysis was therefore 2398 pregnancies (please see flow chart showing data inclusions and exclusions in supplementary figure S1) in 1814 women on cART with membranes ruptured before delivery and information on duration of ROM and HIV viral load near delivery.

Baseline Characteristics

Table 1 shows baseline characteristics of 2398 pregnancies. Almost 80% of pregnancies were in Black African women, and in three-quarters HIV infection was diagnosed prior to this pregnancy. Median interval from last reported HIV viral load to delivery was 22 days (IQR: 9, 37days). Overall, HIV viral load near delivery was undetectable in 89%, and CD4 count was ≥500 cells/μL in 39% of pregnancies. About half of these pregnancies were conceived on cART. The median treatment duration among those initiating cART in pregnancy was 16 weeks (IQR: 13, 20 weeks). More than two-thirds of these pregnancies ended in a vaginal delivery, the majority of which were planned, and 12% of births were preterm (<37 weeks gestation) (Table 1). There were no significant differences in baseline characteristics of pregnancies between those with ROM ≥4 hours and those with ROM <4 hours, except for gestation (16.4% with ROM ≥4 hours were delivered preterm compared with 7.2% with ROM <4 hours, p<0.001) and mode of delivery (52.9% of pregnancies where ROM was ≥4 hours ended in vaginal delivery compared with 83.7% where ROM was <4 hours, p<0.01); the differences in gestation and mode of delivery were similar in the sub-group of pregnancies in women delivering with undetectable viral load [data not shown].

Duration of ROM and MTCT in pregnancies delivered at term

In the 88.2% of pregnancies delivered at term (2116/2398), median duration of ROM was 3 hours 30 minutes (IQR: 1hr, 8hr); 11.2% (238/2116) of these deliveries had ROM duration reported as less than 15 minutes, 3.4% (71) greater than 24 hours, and 1.1% (24) greater than 48 hours. Figure 1 shows the skewed distribution of ROM duration in pregnancies delivered at term. There was no annual trend in the proportion of pregnancies with duration of ROM ≥4 hours (*p*=0.60).

Infection status was reported for 83% of term infants with delivery viral load available (1678/2032), with eight cases of mother-to-child transmission (MTCT rate 0.48%) (Table 2). The MTCT rate was 0.13% among pregnancies delivered with undetectable viral load (2/1519); 2.05% with viral load 50-999 copies/ml (3/146); and 23.1% with viral load ≥1000 copies/ml (3/13). The overall MTCT rate, regardless of delivery viral load, was not significantly different for pregnancies delivered at term with

ROM ≥4 hours (0.64%, 5/786) compared with those with ROM <4 hours (0.34%, 3/892, OR: 1.90; 95% CI: 0.45, 7.97) (Table 2). Results were similar in term deliveries where viral load was <50 copies/ml: the MTCT rate was 0.14% with ROM ≥4 hours and 0.12% with ROM <4 hours (Table 2) (OR: 1.14, 95% CI: 0.07, 18.27). In pregnancies delivered at term in women with undetectable viral load who had ROM ≥4 hours and <24 hours, the MTCT rate was 0.14% (2/1464), and there were no transmissions in the 55 pregnancies where duration of ROM was ≥24 hours.

Timing of infant infection

Term deliveries

Eight infant infections were reported in term deliveries where infection status was reported (1678/2032). Two of these were in infants born to mothers delivering with an undetectable viral load (see Table 3; Cases 6 and 8) and timing of infant test results suggested intrapartum or postnatal transmission. In cases where maternal HIV viral load was detectable at delivery transmission most likely occurred *in utero* in three (Table 3; Cases 1-3), and *in utero* transmission could not be excluded in a further two (Cases 4 and 5). The other infected infant was born to a woman with high viral load and timing was likely intrapartum (Case 7). Excluding the three likely *in utero* transmissions, there was no evidence of a significant difference in MTCT rates in term deliveries at all viral loads, comparing ROM ≥4 with ROM <4 hours (0.38% (3/784), 0.22% (2/891) respectively, OR: 1.71, 95% CI: 0.28, 10.25). Among those pregnancies with ROM <24 hours (excluding the *in utero* transmissions), the MTCT rate was 0.31% (5/1615), and there were no transmissions in the 60 deliveries with ROM ≥24 hours.

Preterm deliveries

Among the 260 preterm infants, 45.1% (32/71) of those born at <34 weeks and 48.7% (92/189) of those born at 34-36 completed weeks gestation were delivered vaginally. Median duration of ROM was 7 hours (IQR 3, 15): 16 hours (IQR 2, 55) for deliveries at <34 weeks, and 6 hours (IQR 3, 11 hours) for deliveries at 34-36 weeks gestation. Delivery viral load was <50 copies/ml in 75.4% (196/260) of these preterm deliveries, 51-999 copies/ml in 21.5% (56/260), and ≥1000 copies/ml in 3.1% (8/260). Infection status was available for 84.6% (220/260) of preterm infants: the overall MTCT rate was 1.36% (3/220), and there were no transmissions with viral load <50 copies/ml. There was one transmission in 67 preterm deliveries with duration of ROM <4 hours, none in 121 with ROM 4 to <24 hours, and two transmissions in 34 with ROM ≥24 hours. Excluding the two likely *in utero* transmissions (see Table 3, Cases 9 and 10), there were no transmissions where ROM was <24 hours, and one where ROM was ≥24 hours; this transmission occurred in an infant delivered by emergency caesarean section where maternal viral load was 50-399 copies/ml (Table 3; Case 11).

Missing data

Overall, there was no significant difference between infants with known infection status and those where infection status was unreported in terms of the proportion with delivery viral load ≤50 copies/ml (89% (1682/1900) versus 91% (356/392), p=0.62), or the proportion with ROM ≥4 hours (50% (941/1900) versus 51% (199/392), p=0.66). There was no significant difference in MTCT rate between the 4200 excluded pregnancies with infection status available (MTCT rate=0.57% (24/4200) and the study population of 1898 pregnancies with infection status available (MTCT= 0.58% (11/1898), *p*=0.93).

Whether or not membranes were ruptured was not reported for 18% of pregnancies after exclusions (19% (126/665) in 2007 and 15% (109/747) in 2012, *p*<0.001). There was no significant difference in MTCT rates between pregnancies with duration of ROM reported and those where it was missing (0.56% (11/1978) with ROM duration reported vs 0.40% (7/1757) with missing ROM duration, p=0.49). There was also no significant difference between these groups in terms of viral load, CD4 count, ethnic group, timing of HIV diagnosis, timing of cART initiation or mode of delivery [data not shown]. However there was a difference in the proportion of preterm deliveries between the two groups: 12% (282/2398) with ROM duration reported were preterm, compared with 22% (449/2025) of deliveries with missing ROM duration *(p*<0.001).

Discussion and Conclusion

Main Findings

There was no evidence of an association between duration of ROM and MTCT in over 2000 pregnancies in HIV-positive women on cART where data was available; in pregnancies delivered at term with an undetectable viral load the MTCT rate was 0.12% with ROM <4 hours and 0.14% with ROM ≥4 hours (OR: 1.14). Similarly, there was no evidence of an association between duration of ROM and MTCT in all term deliveries (i.e. including detectable and undetectable maternal viral loads). Overall, the MTCT rate was very low (0.46%), and similar to the rate of 0.57% recently reported for the cohort as a whole in the period 2007-11.[1] The emergency caesarean section rate in pregnancies where membranes were ruptured was notable at around a third; the finding of no increased risk of MTCT in women with duration of ROM ≥4 hours supports a normalised approach to obstetric care in women taking cART who are in labour at term with ruptured membranes. There was no evidence that the proportion of pregnancies with duration of ROM ≥4 hours had increased over the study period, which suggests that there were no substantial changes in practice or reporting characteristics over time. The 12% preterm birth rate was substantially higher than the

7.1% rate nationally,[15] but similar to recently published data from the cohort as a whole,[1] and in line with other European and American data on women on cART in pregnancy.[16]

Strengths and Limitations

Because of the high uptake of antenatal HIV screening[17] and high study response rates [unpublished data, NSHPC], the majority of HIV positive pregnant women in the UK and Ireland are diagnosed prior to delivery and reported to our comprehensive surveillance study. To our knowledge this is the largest study to explore the effect of duration of ROM on MTCT rates in the cART era. Detailed reports are made to the study at several time points for each mother-child pair ensuring well-reported data on ART, delivery characteristics, viral load and infant infection status, and enabling the sub-analysis of MTCT rates in women on cART with undetectable viral load; currently this is the only group in the UK for whom vaginal delivery is recommended.

Due to very low MTCT rates in recent years, the number of infected children was small, precluding further subgroup analyses. Infection status was available for 83% of infants, with missing data largely due to reporting delay for more recent deliveries and not likely to result in substantial bias, as reported previously.[1] In this analysis there was no significant difference, in terms of delivery viral load or duration of ROM, between infants with and without infection status reported. The small number of transmissions resulted in loss of precision in the estimates and wide confidence intervals for some of the calculated odds ratios. Similarly, small numbers in some sub-groups meant the data were not suitable for multivariable analyses. Furthermore the distribution of duration of ROM was highly skewed; ROM duration was therefore analysed as a categorical rather than a continuous variable. The proportion of missing data on duration of ROM decreased over time, probably due to gradually improving completion rates after the data field was added to reporting forms.

Although transmissions classified as *in utero* most likely occurred before delivery (and before ROM) it is possible that transmission could have occurred at the time of delivery if duration of ROM was prolonged. However findings were similar whether or not these likely *in utero* transmissions were included. Clinical indications for emergency caesarean section were not considered in this analysis; this information was not well reported. Deliveries with duration of ROM ≥4 hours were more likely to be emergency caesarean sections than those with duration <4 hours. It is possible that some clinicians proceed to emergency caesarean section if duration of ROM is prolonged because of a perception of increased risk, although several studies have shown that caesarean section confers no benefit in terms of MTCT in women delivering with undetectable HIV viral load.[1,18–20] However, longer duration of ROM may be associated with other obstetric indications for expediting delivery.

Interpretation

These data from our national surveillance study confirm and strengthen previous findings that duration of ROM does not increase the risk of MTCT in women on cART.[11,12] The emergency caesarean section rate for singleton live births among all diagnosed HIV-positive women delivering in 2007-2011 was 24.7%,[1] higher than the national rate for England of 14.4% in 2012-13.[20] Our data provide further support for national guidelines which recommend that for HIV-positive women with undetectable viral load at term, obstetric management should follow the same principles as for the uninfected population.[4]

Women living with HIV are at increased risk of preterm birth.[21] There are no published data to inform the optimal management of women with preterm pre-labour rupture of membranes prior to 34 weeks, and current guidelines recommend management on a case-by-case basis: the benefits of delaying labour weighed against the risk of MTCT.[4] It is not possible to draw firm conclusions from the relatively small number of preterm deliveries in this analysis, although it is reassuring that there were no transmissions in pregnancies delivered preterm with an undetectable viral load despite the much longer duration of ROM in some of these cases, which was probably associated with the administration of corticosteroids.

Conclusion

MTCT does not appear to be associated with duration of ROM in HIV-positive women delivering at term on effective cART. As the normalisation of vaginal delivery for women with undetectable HIV viral load continues, we expect the number delivering with duration of ROM ≥4 hours to increase, and future analyses will be based on a larger population. This is especially important for exploring the relationship between gestation at onset of labour, duration of ROM and MTCT for women with preterm pre-labour ROM, who present obstetricians with the greatest challenge when deciding whether to delay delivery to optimise fetal maturation. In the current era of well-tolerated and highly effective ART, with an overall MTCT rate of 0.05% in women delivering on cART with an undetectable viral load,[1] we are moving towards the goal of ensuring that women living with HIV who have fully suppressed viral load have the same obstetric options as their uninfected peers.

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Disclosure of interests

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Contribution to authorship

HP and CLT carried out the statistical analyses. All authors contributed to developing the concept of the article which was drafted by LB, HP and CLT. HP, LB, AdR, KF, KH, GT, PT, CLT contributed to interpreting the results, and critically revising the article. PAT is responsible for the NSHPC and is the guarantor.

Details of ethics approval

The National Study of HIV in Pregnancy and Childhood has London Multi-Centre Research Ethics Committee approval (MREC/04/2/009).

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Table 1: Baseline characteristics of 2398 eligible* pregnancies in 1814 women delivered 2007-2012

Characteristic	N	%
Maternal age (years)		
<20	37	1.5
20-29	799	33.3
30-39	1426	59.5
≥40	136	5.7
Maternal ethnic group		
White	326	13.6
Black African	1875	78.3
Other	195	8.1
Mode of acquisition		
Heterosexual	2195	97.0
IDU-related	33	1.5
Other	34	1.5
Timing of HIV diagnosis		
Before pregnancy	1779	74.2
During pregnancy	619	25.8
Viral load nearest delivery (copies/ml)		
<50	2038	88.9
50-399	202	8.8
400-999	29	1.3
1000-9999	9	0.4
≥10,000	14	0.6
CD4 near delivery (cells/mm3)		
≥500	891	38.7
350-499	752	32.6
200-349	491	21.3
<200	170	7.4
Mode of delivery		
Emergency CS	757	31.6
Planned vaginal	1569	65.4
Unplanned Vaginal	72	3.0
Gestation (completed weeks)		
<34	80	3.3
34-36	202	8.4
≥37	2116	88.2

*Singleton livebirths, delivered vaginally or by emergency caesarean section, in mothers diagnosed with HIV during or before pregnancy, on cART in pregnancy, membranes ruptured prior to delivery and duration of ROM reported.

cART: combination antiretroviral therapy; ROM: rupture of membranes

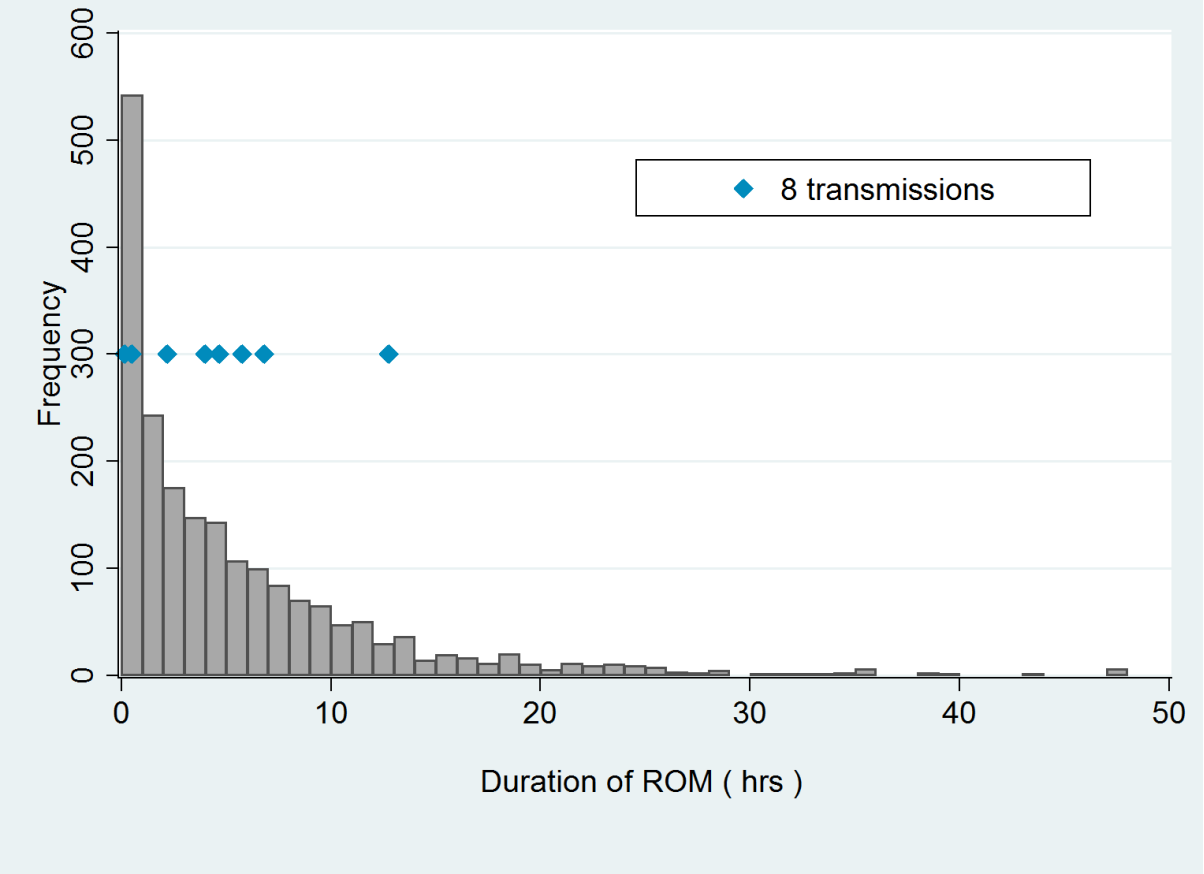

Figure 1: Distribution of duration of ROM in women delivering at term with ROM <48 hours

Table 2: Mother-to-child transmission rates by duration of ROM among 1678 term deliveries (≥37 weeks)

Duration of ROM	All infants delivered at term	Infants delivered at term with suppressed maternal VL[1]
<4 hour	0.34% (3/892)	0.12% (1/809)
4 to <24 hour	0.69% (5/726)	0.15% (1/655)
≥24 hours	0.00% (0/60)	0.00% (0/55)
Total	0.48% (8/1678)	0.13% (2/1519)

ROM: rupture of membranes; VL: HIV viral load

[1] Viral load <50 copies/ml

Table 3: Cases of mother-to-child transmission in women delivering 2007-2012 with duration of rupture of membranes reported (ordered by gestation, timing of infection then maternal VL)

	Gestation at delivery (weeks)	Duration of ROM (hrs)	Mode of delivery	Maternal HIV VL (copies/ml)	Likely timing of infant infection
Term deliveries					
Case 1	≥37	<4	Pl VD	50-399	*In utero*
Case 2	≥37	4 to <24	Em CS	50-399	*In utero*
Case 3	≥37	4 to <24	Unpl VD	≥10,000	*In utero*
Case 4	≥37	<4	Pl VD	50-399	*In utero*/intrapartum
Case 5	≥37	4 to <24	Em CS	≥10,000	*In utero*/intrapartum
Case 6	≥37	<4	Pl VD	<50	Intrapartum
Case 7	≥37	4 to <24	Em CS	≥10,000	Intrapartum
Case 8	≥37	4 to <24	Pl VD	<50	Intrapartum/postnatal
Preterm deliveries					
Case 9	<34	≥24	Unpl VD	≥10,000	*In utero*
Case 10	34-36	<4	Em CS	≥10,000	*In utero*
Case 11	34-36	≥24	Em CS	50-399	Unknown

ROM: rupture of membranes; Pl: planned; Unpl: unplanned; VD: vaginal delivery; Em: emergency; CS: caesarean section; VL: viral load