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Neonatal deaths among infants born to women living with HIV in the UK and Ireland 1998-2017

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Running head (max 40 characters): Neonatal deaths in HIV-exposed infants

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Abstract

Objective(s): To estimate the incidence of neonatal mortality among infants born to women living with HIV in the UK and Ireland in 1998-2017, describe causes of neonatal death (NND) and examine risk factors.

Design: Population-based surveillance of pregnancies in diagnosed women living with HIV and their infants in the UK and Ireland.

Methods: Estimated yearly incidence of NND was reported for 1998-2017 and causes coded using the World Health Organization International Classification of Perinatal Mortality. Risk factor analyses used multivariable logistic regression, including delivery year, maternal origin, maternal age, delivery CD4 count and viral load (VL), antiretroviral therapy (ART) at conception, preterm delivery (PTD), injecting drug use and infant sex.

Results: There were 20,012 live-born infants delivered to 12,684 mothers in 19,601 pregnancies. The overall neonatal mortality rate was 4.10 per 1000 livebirths (95%CI, 3.2-5.0), which was higher than that of the general population. Prematurity was the leading cause

of death followed by congenital abnormality. Most NND occurred on the first day of life. ART at conception was associated with significantly reduced NND risk. In a restricted 2007-2017 analysis including VL, PTD and detectable maternal VL were associated with significantly increased NND risk.

Conclusions: The vertical transmission rate in the UK, at 3 per 1000, is now lower than the neonatal mortality rate among infants born to women with HIV. More research is needed to investigate the complex relationship between ART, preterm delivery and neonatal death in order to improve all perinatal outcomes.

Key words: HIV; neonatal mortality; perinatal outcomes; newborn; pregnancy

Introduction

There are around 1000 pregnancies in women living with HIV (WLWH) in the UK and Ireland every year (1). Vertical transmission (VT) rates have now stabilised at around 3 per 1000 live births among diagnosed women (2, 3), with similar rates reported from other high-income countries (HICs) (4-6). Meanwhile, the PROMISE trial has reported overall VT of 1.3% at 24 months in a breastfeeding population on ART in sub-Saharan Africa and India (7). In the UK today, most pregnant WLWH have an established HIV diagnosis and are on suppressive antiretroviral therapy (ART) before pregnancy (2). Trends in the use of ART have changed, with the proportion on ART at conception increasing from 40% in 2007-2011 to 70% in 2015-2016 (2, 8).

The goal of providing treatment and care to pregnant women with HIV is to optimise the health of both mother and baby. In the context of declining VT, additional scrutiny of other adverse birth outcomes has taken place, including preterm delivery (PTD), infants small-for-gestational age and stillbirth (9-13) alongside calls for better pregnancy pharmacokinetic and safety data for newer antiretroviral drugs (14, 15). Observational studies and clinical trials in lower and middle income countries (LMICs) and HICs have shown that adverse pregnancy outcomes differ according to ART regimen (10, 16-18). Timing of initiation of ART may also be important, as demonstrated by a large systematic review and other studies that found that pregnant women initiating ART before conception had significantly greater probability of delivering preterm than those starting during pregnancy (9-12).

We have recently investigated stillbirths among WLWH using national surveillance data from the UK and Ireland. During 2007-2015, there was a stillbirth rate of 8.5 (95% confidence interval [CI], 6.9, 10.5) per 1000 births, with a slight but non-significant decline over time; risk factors included older maternal age, primiparity, pre-eclampsia, diabetes and CD4 count <350 cells/mm^3, but not conception on ART (19). The overall stillbirth rate seen in the general population of England and Wales over the same time period was 5.2 per 1000

births ; even after adjusting for maternal region of origin the study population stillbirth rate was still 29% higher than that of the general population (19).

In the UK general population the neonatal mortality rate has declined to 1.72 deaths per 1000 livebirths in 2016 (20), but is still one of the highest in Western Europe (21). UK data shows a large proportion of newborn deaths are due to immaturity-related conditions or congenital abnormalities (22). Quality improvement programmes such as the 'Each Baby Counts' initiative of the Royal College of Obstetricians and Gynaecologists and the National Perinatal Epidemiology Unit's 'Perinatal Mortality Review Tool' aim to increase understanding and prevent future neonatal mortality nationally.

Our aim was to extend our previous research on stillbirths in women with HIV by examining national HIV surveillance data to estimate the incidence of neonatal mortality among infants born to WLWH in the UK and Ireland in 1998-2017, to describe causes of neonatal death and to examine risk factors and timing of neonatal death.

Methods

The National Surveillance of HIV in Pregnancy and Childhood (NSHPC) has conducted comprehensive, active population-based surveillance, with data on all pregnancies in diagnosed WLWH in the UK and Ireland, their infants and any children diagnosed with HIV for nearly 30 years. In 2018 the NSHPC became a part of the Infectious Diseases in Pregnancy Screening Programme (IDPS) and became known as the Integrated Screening Outcomes Surveillance Service (ISOSS). Submitting data to ISOSS is part of the IDPS service specification (23) by named 'respondents' in all maternity and paediatric units (e.g. antenatal screening coordinators or paediatricians) using a secure online portal. Data are collected without patient consent with PHE Regulation 3 approval (24). Maternal information collected includes maternal demographics and diagnosis, pregnancy and clinical characteristics, delivery details and pregnancy outcome. Paediatric data collected includes infant follow-up status, test results and congenital abnormalities and/or infections.

All livebirths to women diagnosed with HIV on or before the day of delivery in 1998-2017 and reported to the NSHPC by the end of 2018 were included. Neonatal deaths are routinely reported by both maternity and paediatric respondents, but data on causes of neonatal death are only collected on paediatric follow-up forms, which may not be completed for very early neonatal deaths. Details of coroner's reports were occasionally provided by respondents but are not routinely requested. Information differentiating primary and secondary cause of death is not routinely collected by ISOSS. For this analysis, causes of death were classed as primary and secondary causes according to respondent classification if available; if unspecified, the first and second reported causes were assumed to be the primary and secondary cause respectively, with any additional causes of death classed as 'other causes'. Each cause of death was individually assigned a World Health Organization International Statistical Classification of Diseases and Related Health Problems – Perinatal Mortality (ICD-PM) code (25). All specific neonatal death causes were grouped using the WHO ICD-PM groupings (see supplementary table, http://links.lww.com/QAD/C333).

Definitions

The Mothers and Babies Reducing Risk by Audits and Confidential Enquires (MBRRACE) definition of neonatal death was used: 'A live born baby, who died before 28 completed days after birth' (20). Gestational age at delivery was reported in completed weeks. Preterm was defined as a pregnancy that completed less than 37 weeks gestation and extremely preterm as less than 28 weeks. An HIV RNA viral load of >50 copies/ml was considered detectable, with a delivery viral load and delivery CD4 count defined as within 30 days of delivery. 'Diabetes' was defined as gestational diabetes as well as pre-existing diabetes as reported by the respondent. Maternal co-infection included mothers infected with either hepatitis B, hepatitis C or syphilis only as reported by the respondent.

Statistical analyses

Rate of neonatal death was calculated from 1998-2017 per 1000 livebirths (number of deaths/ number of livebirths x 1000) and reported with 95% CI. Differences in proportion were tested using chi-squared tests. Univariable and multivariable logistic regression models were fitted to investigate risk factors for neonatal mortality, restricted to singleton births and conducted on a complete case basis. Robust standard errors were used to account for repeated pregnancies in the same mother. For maternal co-infection and pre-eclampsia (routinely collected from 2008 and 2005 respectively), only univariable analyses were carried out. For the adjusted model, calendar year, maternal age and region of origin, delivery CD4 count, delivery viral load, injecting drug use (IDU) history, PTD and infant sex were included *a priori* due to known associations with neonatal mortality (20, 26-30). There was a high number of missing observations for delivery viral load (8,358/19,601), concentrated in the earlier years of the study period. Delivery viral load was therefore excluded from the main adjusted model, with a further multivariable analysis conducted restricted to 2007-2017, a time period with improved reporting of delivery viral load (main model plus delivery viral load).

P-values of <0.05 were regarded as having statistical significance. Statistical analyses were performed using Stata version 15.1 (StataCorp, College Station, TX, USA).

Results

In 1998-2017, there were 20,012 live-born infants delivered to 12,684 mothers in 19,601 pregnancies reported to the NSHPC and meeting our inclusion criteria. Median maternal age at delivery was 31 (interquartile range [IQR] 27-35) years, three-quarters of pregnancies were to mothers born in Sub-Saharan Africa and 15% to mothers born in the UK or Ireland, and 99.4% of mothers received ART during pregnancy (Table 1). Infant characteristics are presented in Table 2, for live-born infants surviving the neonatal period and for those with neonatal death. The overall rate of neonatal death was 4.10 per 1000 livebirths (95% CI, 3.2-5.0), and 4.80 per 1000 livebirths in 2013-2017. There were some significant differences between infants who died in the neonatal period and those who survived, with a greater proportion of mothers with a detectable delivery viral load and pre-eclampsia, PTD, low birthweight (LBW) and congenital abnormality in the former (Table 2).

Causes of neonatal death

Among the 20,012 live-born infants, there were 82 neonatal deaths, with no reported cause of death for 18 (22%). In total there were 104 individual causes of death reported among the remaining 64 cases of neonatal death. Figure 1 is a mosaic plot that visually represents the relative frequencies of causes of death (grouped by ICD-PM classification, with each group represented by a different colour) by primary, secondary and other causes of death for these 64 neonates; frequencies of each cause of death within each group are presented in the Supplementary Table, http://links.lww.com/QAD/C333. LBW and prematurity was a cause of death in 44% (28/64) cases, and was also the leading primary cause of death (Figure 1). Congenital malformations, deformations and chromosomal abnormalities was the second most common cause of death (34%, 22/64), with trisomy 18 the most common abnormality (6 cases) (Supplementary Table, http://links.lww.com/QAD/C333). Two-thirds of the 64 primary causes of death (42/64) were due to either LBW and prematurity or congenital abnormality. Six neonates had necrotising enterocolitis (NEC) reported as a cause of death, of whom five were born at ≤31 gestational weeks. Among the 15 deaths attributed to infections, septicaemia was the cause of death in six cases, HIV in three, TB in two, disseminated HSV in two and meningitis in one case.

Timing of neonatal death

Of the 82 neonatal deaths, 26 (32%) occurred within the first day of life (day 0); of these 26, 11 (42%) were due to prematurity. After completion of the first day of life there was a general and gradual decreased risk of neonatal death. Figure 2 shows the distribution of neonatal deaths by gestational age for the 81 newborns with gestational age available. Half of the neonatal deaths (41/81) were among extremely preterm infants and 81% (64/81) were preterm.

Risk factor analysis

In univariable analyses, PTD, pre-eclampsia and detectable delivery viral load were statistically significantly associated with neonatal death (Table 3). In the main multivariable model involving 15,866 mother-infant pairs, PTD was associated with a highly increased odds of neonatal mortality (adjusted odds ratio [AOR] 25.9, 95% CI 14.1-47.5), whilst ART at conception was associated with a reduced odds (AOR 0.52, 95% CI 0.29-0.94) after adjusting for calendar year, maternal origin, maternal age, CD4 count at delivery, maternal IDU history and infant sex (Table 3). In the model restricted to 2007-2017 including 7072 mother-infant pairs (27 neonatal deaths), odds of neonatal death was significantly increased for infants born preterm (AOR 28.0, 95% CI 11.1-70.5) and for those born to mothers with detectable delivery viral load (AOR 5.04, 95% CI 1.97-12.9). In this restricted model, year of delivery per one year increase was also associated with a significantly increased odds of neonatal death (AOR 1.18, 95% CI 1.02-1.35).

Discussion

In this analysis, based on national surveillance of HIV in pregnancy, just over four in every 1000 live-born infants of WLWH in the UK and Ireland died in the neonatal period in 1998-2017. In our study population, 69% of mothers had an established HIV diagnosis from before

pregnancy, 42% were on ART at conception and nearly two-thirds had delivery CD4 counts higher than 350 cells/mm^3. With respect to adverse birth outcomes, 13% of deliveries were preterm and 15% of infants had LBW.

The neonatal mortality rate among infants born to women with HIV was not only higher than that reported in the general population in England and Wales (3.24 per 1000 livebirths in 1998-2016) (31) but findings from our multivariable analysis (2007-2017) also indicated that risk of neonatal death may have increased in recent years. The main cause of neonatal mortality was prematurity (69% of newborns who died were born at <35 weeks gestation), with other immaturity-related conditions such as respiratory distress syndrome, pulmonary hypoplasia and intraventricular haemorrhage also recorded. This is consistent with the general population where most neonatal deaths are due to immaturity-related conditions (32). In a recent NSHPC analysis, PTD was investigated in 6073 live-born singleton infants exposed to either a boosted PI- or non-nucleoside transcriptase inhibitor (NNRTI)-based regimen in 2007-2015; the overall PTD rate was 10.4%, with a small but significantly increased risk in women conceiving on ART (aOR 1.27, 95% CI 10.01,1.61)(12). Complex associations were observed between different ART regimens and PTD, with significantly increased odds in women conceiving on ritonavir-boosted lopinavir (LPV/r) versus NNRTI-based regimens (regardless of maternal CD4 count) and in women conceiving on other boosted PI-based regimens versus NNRTI-based regimens with a CD4 count below 350 cells/mm^3 (12). The overall rate of PTD in this analysis declined from 11.6% in 2007-2009 to 9.3% in 2013-2015 (12), a time period largely overlapping with that for our restricted analysis (2007-2017).

Congenital abnormalities were reported as a cause of death in around 30% of cases. This is a very similar proportion to the general population; 33% in 2016 (20). This is reassuring as the number of mothers ≥40 years of age in the study population is increasing over time (30) and there is a known association between increasing maternal age and increasing risk of congenital abnormality (33).

Nine percent of the neonatal deaths with known cause were due to NEC, at least partly reflecting the large proportion of preterm births in this group, as NEC is most common in preterm infants. However, a case-control study among premature neonates admitted to a single neonatal unit found a strong association between incidence of NEC and being born to a mother living with HIV (AOR 6.63, 1.26-34.8) (34). Higher mortality among preterm infants who were HIV-exposed and uninfected with NEC than among HIV-unexposed infants with NEC has also been observed (35).

In our study, 25% of the neonatal deaths were attributed to infection (most commonly septicaemia), which is potentially higher than expected given that the equivalent figure in the general population in 2016 was 7.6% (20). Two cases of disseminated neonatal HSV (36), which is associated with a high fatality rate even with antiviral therapy (37), were reported. Incidence of neonatal HSV in the UK has increased over the past 20 years to an estimated 17.5 per 100,000 in a recent study (38) and HIV infection is associated with higher HSV prevalence and more frequent and longer-lasting HSV reactivation(39). Women with active genital lesions have a greater risk of vertical transmission (40) and clinicians should be extra

cautious in these cases. The British Association for Sexual Health and HIV (BAASH) guidelines recommend all pregnant WLWH with a history of genital herpes should be started on acyclovir treatment from 32 weeks of gestation (41). Infants who are HIV-exposed and uninfected have been reported to be at increased risk of infectious disease morbidity in both LMICs and HICs, including more severe and uncommon infections (42-44). Mechanisms are not well understood but could involve the interaction between the unique exposures and altered immunity of these infants (34, 45).

The proportion of pregnant WLWH who conceive on ART has been increasing over time in the UK and is now around 70% (8), compared with 42% for the whole 20 year period assessed here. Conception on ART was associated with a substantially lower risk of neonatal death (AOR 0.52, 95% CI 0.29-0.94) in our analysis adjusting for factors including calendar year, maternal CD4 count and age. Whilst several studies (including our own) have shown that ART use at conception may be associated with increased risk for adverse birth outcomes i.e. PTD and LBW, this has not been shown for neonatal mortality, although data are very limited (9, 10) (12). Another large, population-based surveillance study, the Tsepamo Study in Botswana, has also reported no significant difference in risk of neonatal mortality between infants whose mothers conceived on ART versus those exposed later in pregnancy (1.7% versus 1.3%) (9, 10); the study also reported significantly increased risk of neonatal death associated with maternal use of zidovudine +lamivudine+nevirapine and of zidovudine+lamivudine+LPV/r versus tenofovir+ emtricitabine+ efavirenz. Due to small numbers of neonatal deaths, it was not possible to examine specific ART regimens in our analyses.

In the 2007-2017 restricted multivariable analysis model, detectable viral load at delivery was associated with a five times increased odds of neonatal mortality. An unsuppressed viral load may be an indicator for poor maternal health and an adverse uterine environment, late diagnosis and poor engagement in healthcare (29, 46, 47). A large systematic review reported a non-significant, but positive association between untreated maternal HIV and neonatal mortality, but the available data were heterogeneous and limited (29). Sustained maternal viral load suppression through effective ART is a key clinical and public health goal, and will not only improve maternal health and prevent onward transmission but may also, as our findings suggest, reduce risk of neonatal death.

Advanced maternal age is a well-recognised risk factor for adverse birth outcomes (48), including in WLWH. We have previously reported increased risk of stillbirth in women aged ≥40 years compared to younger women in the NSHPC (AOR 2.39, p-value 0.004) (30). In the UK overall, the rate of neonatal mortality in infants of women aged ≥40 years increased from 2.46 to 2.69 per 1,000 live births between 2014 and 2016 (20). Although not statistically significant in adjusted analyses here, the neonatal mortality rate was highest in older mothers (>40 years) at 4.67 per 1000, which is concerning given our ageing population (30). Although we have previously reported increased risk of stillbirth in women born in Asia and Africa (excluding South Africa) (19), maternal region of origin was not shown to be associated with risk of neonatal death here; however, this may have been due to larger groupings used to ensure regression model stability.

Strengths of this analysis include the comprehensive population-based coverage of all women diagnosed with HIV and their infants, providing a study dataset representative of the whole population of women with diagnosed HIV delivering in the UK and Ireland. However, the analysis has limitations, including the inability to adjust for known risk factors associated with neonatal death such as maternal smoking and obesity (49, 50) that are not routinely collected. Although data are lacking on prevalence of smoking in pregnant WLWH in the UK, a survey in England reported that 12% of WLWH were current smokers (51), whilst in the general pregnant population, prevalence of smoking was 11% in 2017 (a decrease from 16% in 2006) (52). An analysis based on Scottish national data in 1999-2009 estimated that the population attributable fraction of maternal current smoking for neonatal death was 6.7% (50). Whilst pre-pregnancy weight and pregnancy weight gain (inadequate to excessive) in WLWH are current topics of interest, particularly in relation to type of antiretroviral regimen (53, 54), the prevalence of obesity in pregnant WLWH in the UK is uncertain, but may be expected to be high based on a prevalence of 38% of WLWH in one English study (55). This may be of concern, given that a large meta-analysis reported a moderate increase in relative risk (RR) of neonatal death per 5 unit increase in maternal body mass index (BMI) (RR 1.15, 95% CI 1.07, 1.23) (56). We started to routinely collect data on maternal height and weight in ISOSS in 2021, which will strengthen future analyses of adverse pregnancy and perinatal outcomes.

Data on co-infections have only been routinely reported to the NSHPC from 2008 and, whilst collection of pre-eclampsia data started in 2005, there was a large amount of missing data and thus neither variable was included in the multivariable analyses. The high number of missing delivery viral load results from the earlier years of surveillance required exclusion of this variable from the main multivariable risk factor model. Delivery viral load was only available for 27 of the neonates who died. This is partly explained by the high proportion of PTD and the complex nature of these cases, e.g. delivery may have occurred prior to a scheduled "delivery" viral load. Although causes of neonatal deaths have been routinely collected during paediatric follow-up, some neonatal deaths were only reported via maternal outcome forms with no cause of death given.

This analysis adds to the limited evidence-base on neonatal deaths in infants born to WLWH in HICs. The VT rate in the UK, at around 3 per 1000 live births, is now lower than the neonatal mortality rate, whilst the stillbirth rate is around 8.5 per 1000 (19). This work demonstrates the need to focus on improvement of all perinatal outcomes and not just on averting new perinatal infections, and to conduct future research and surveillance to understand better the risk factors experienced in this population in order to identify potential interventions to reduce extended perinatal mortality. Further work is needed to fully understand the relationships and mechanisms between maternal HIV disease, other maternal characteristics, ART exposure and PTD in order to reduce this adverse outcome, which our data indicate remains the major cause of neonatal deaths. This study has also highlighted the importance of supressed maternal viral load during pregnancy in potentially reducing risk of neonatal death. This underscores the necessity to identify the safest, most tolerable and

effective regimens for pregnant WLWH to maximise maternal and child health, including scenarios where HIV diagnosis may occur late, as well as to enable early diagnosis of women living with HIV (ideally prior to pregnancy), to support and facilitate women's engagement with health services and to support ART adherence.

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Roles of the authors

Conceptualisation: CT, HP; Data curation: HP; Analyses: HY; Funding acquisition: CT, HP; Writing – original draft preparation HY; review and editing CT, HP, HY.

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Figure 1. Mosaic plot displaying causes of neonatal death by primary, secondary and other 1-3

Footnote: the area of each coloured block indicates the relative frequency of each observation

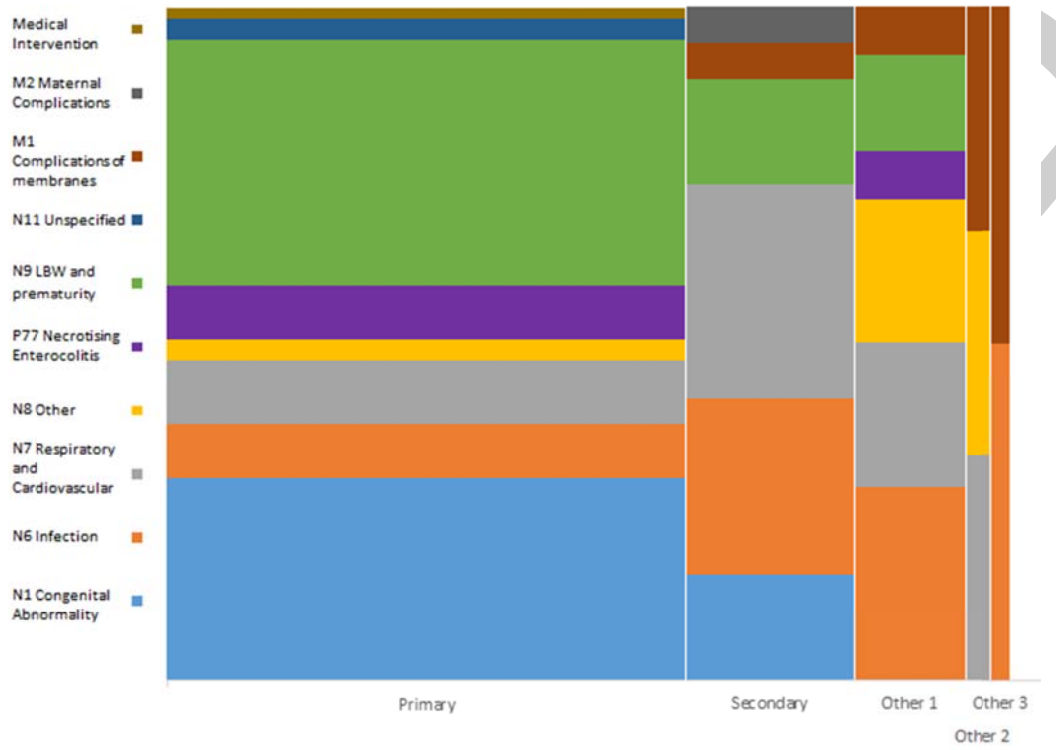

Figure 2. Distribution of neonatal death by gestational age at birth (n=81)

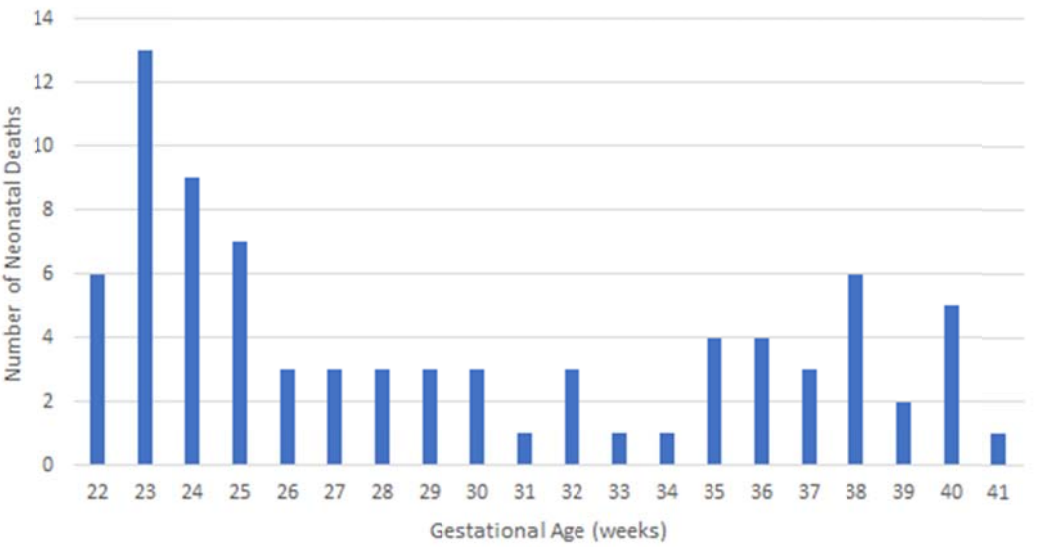

Table 1 – Maternal and pregnancy characteristics by outcome

	Pregnancies with liveborn infants surviving the neonatal period ***n=19,522***	**Pregnancies with neonatal deaths** ***n=79***	**P-value***
	n (%)		
Maternal age at delivery (years), n=19546			0.551
<20	387 (2)	1 (1)	
20-24	2022 (10)	9 (12)	
25-29	4897 (25)	21 (27)	
30-34	6352 (33)	22 (28)	
35-39	4527 (23)	16 (21)	
≥40	1283 (7)	9 (12)	
Maternal region of origin, n=19385			0.607
UK/Ireland	2903 (15)	14 (18)	
Africa	14492 (75)	54 (70)	
Other	1913 (10)	9 (12)	
Timing of HIV diagnosis, n=19601			0.862
Before pregnancy	13414 (69)	55 (70)	
During pregnancy	6108 (31)	24 (30)	
ART at conception, n=18780			0.194
Yes	7811 (42)	25 (34)	
No	10896 (58)	48 (66)	
Delivery CD4 count (cells/mm^3), n=17193			0.384
≥500	6349 (37)	20 (29)	
350-499	4663 (27)	18 (26)	
200-349	4152 (24)	22 (32)	
<200	1960 (11)	9 (13)	
Delivery viral load (copies/ml), n=11352			**<0.001**
<50	8644 (76)	19 (44)	
≥50	2665 (24)	24 (56)	
Syphilis co-infection, n=8961			0.417
No	8774 (98)	39 (100)	
Yes	148 (2)	0	
Pre-eclampsia, n=14313			**0.018**
No	13873 (97)	39 (91)	
Yes	440 (3)	4 (9)	
Pre-existing and Gestational Diabetes, n=19601			0.202
No	19127 (98)	79 (100)	

Yes	395 (2)	0	
Maternal co-infection with HBV, HCV or Syphilis, n=19601			0.529
No	18796 (96)	75 (95)	
Yes	726 (4)	4 (5)	

** Chi-squared statistical test*

Table 2: Infant characteristics, by outcome

	Liveborn infants surviving the neonatal period n=19,930	**Neonatal deaths n=82**	**P-value***
	n (%)		
Child birth year, n=20,012			0.649
1998-2002	2012 (10)	10 (12)	
2003-2007	5996 (30)	21 (26)	
2008-2012	6743 (34)	26 (32)	
20013-2017	5179 (26)	25 (30)	
Gestational age (weeks), n=19801			**<0.001**
≥37	17122 (87)	17 (21)	
35-36	1306 (7)	8 (10)	
32-34	750 (4)	5 (6)	
≤31	542 (3)	51 (63)	
Birthweight (g), n=18493			**<0.001**
≥2500	15794 (85)	12 (19)	
1500-2499	2228 (12)	14 (22)	
<1500	471 (3)	37 (59)	
Sex, n= 19946			0.956
Male	10031 (51)	39 (52)	
Female	9834 (49)	36 (48)	
Congenital abnormality, n=20012			**<0.001**
None	19025 (95)	50 (61)	
One	841 (4)	25 (30)	
Multiple	64 (1)	7 (9)	

Table 3. Multivariable analysis of risk factors for neonatal death

			1998-2017 Main Model		Restricted analysis 2007-2017 including delivery viral load	
	Total livebirths in main model	Neonatal death rate per 1000 livebirths	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	n=15866	3.72	n= 15,866		n=7072	
Calendar year of delivery						
Per one year increase			0.99 (0.93-1.05)	1.02 (0.95-1.09)	1.07 (0.93-1.22)	1.18 (1.02-1.35)
Maternal origin						
UK + Europe	3016	3.32	1.00	1.00	1.00	1.00
Other	12,850	3.81	1.15 (0.58-2.27)	1.39 (0.65-2.98)	2.09 (0.63-6.93)	2.97 (0.70-12.7)
Maternal age group (years)						
≤24	1925	1.56	0.39 (0.12-1.26)	0.37 (0.11-1.21)	0.36 (0.05-2.67)	0.35 (0.05-2.48)
25-39	12,871	3.96	1.00	1.00	1.00	1.00
≥40	1070	4.67	1.18 (0.47-2.96)	1.25 (0.49-3.18)	1.21 (0.36-4.04)	1.25 (0.40-3.90)
ART at conception						
No	9082	4.54	1.00	1.00	1.00	1.00
Yes	6784	2.65	0.59 (0.34-1.02)	0.52 (0.29-0.94)	0.49 (0.22-1.09)	0.69 (0.25-1.86)
CD4 count at delivery (cells/mm^3)						
≥350	10,167	3.05	1.00	1.00	1.00	1.00
<350	5699	4.91	1.61 (0.97-2.69)	1.29 (0.74-2.22)	1.93 (0.90-4.11)	1.27 (0.58-2.78)
Maternal history of IDU						
No	15,543	3.60	1.00	1.00	1.00	1.00
Yes	323	9.29	2.59 (0.80-8.35)	1.76 (0.47-6.49)	2.11 (0.28-15.7)	1.98 (0.20-19.2)
Preterm delivery						
No	14,089	0.99	1.00	1.00	1.00	1.00
Yes	1768	25.5	26.3 (14.4-48.0)	25.9 (14.1-47.5)	35.3 (13.3-93.7)	28.0 (11.1-70.5)
Infant sex						
Male	8019	3.87	1.00	1.00	1.00	1.00

Female	7847	3.57	0.92 (0.55-1.54)	0.90 (0.53-1.51)	0.70 (0.32-1.50)	0.73 (0.34-1.58)
Viral load at delivery 2007-17						
Undetectable	5879	1.87			1.00	1.00
Detectable	1193	13.41			7.25 (3.36-15.7)	5.04 (1.97-12.9)
Univariable only						
Pre-eclampsia						
No	13636	2.79	1.00			
Yes	426	3.39	3.39 (1.21-9.53)			
Maternal co-infection with HBV, HCV or syphilis						
No	18,480	3.84	1.00			
Yes	715	5.59	1.46 (0.53-4.02)			