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Stillbirth in women living with HIV delivering in the UK and Ireland: 2007-2015

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UK/Ireland), CD4 count <350cells/mm^3, older maternal age and primiparity. Conceiving on ART did not increase the risk. The stillbirth rates (per 1000 births) by type of ART were 14.3, 11.7, 8.3, and 6.0 respectively for NVP+XTC/TDF-, LPV/r+3TC/ZDV-, NVP+XTC/ABC- and NVP+XTC/ZDV-exposed pregnancies (p- value=0.40). The SSR was 129 (95%CI 101, 165) in women with HIV compared with the general population.

Conclusion*:* After adjusting for maternal origin, the stillbirth rate remained higher in women with HIV than the general population. We recommend further studies to understand and prevent this excess.

Keywords: stillbirth; human immunodeficiency virus; adverse pregnancy outcome; antiretroviral therapy.

Introduction

The causes of stillbirth are multifactorial, vary by settings and are not fully understood. Studies conducted in the era before combination antiretroviral therapy (ART) showed that untreated maternal HIV is associated with adverse birth outcomes, including stillbirth[1]. In the current era, with newer generations of antiretroviral drugs and increasing proportions of women on ART at conception, it is unclear whether women with HIV are still at risk. Studies on stillbirth in women with HIV are scarce but recent findings suggest that the type and timing (pre/post-conception) of ART may also be associated with stillbirth[2-5]. Besides, the extent to which risk factors in the general population may affect women with HIV is uncertain, for example pre-eclampsia and other antenatal comorbidities, infections, primiparity, lifestyle, age, socio-economic deprivation[6-8] and being a migrant (i.e. not born in the country where they give birth). In high income countries migrant women are at elevated risk of delivering a stillborn infant compared with non-migrant women, although the risk varies between different migrant

groups[8,9].

Between 1990 and 2006, the stillbirth rate among women living with HIV in the UK and Ireland was 1.1%, twice as high as that in the general population[10]. Since then, there have been substantial changes in maternal characteristics (e.g. increasing age, greater proportion with established HIV diagnosis at conception, higher CD4 counts) and antenatal ART use[11]. We used data from a UK population-based surveillance study in women with HIV delivering in the UK and Ireland between 2007 and 2015 to (1) describe stillbirth rates in women with HIV stratified by type of ART and (2) evaluate risk factors. In the UK a large proportion of pregnant women with HIV are migrants from world regions with an increased risk of stillbirth[11]. A further objective was therefore to compare stillbirth rates in women with HIV with the general population using national data, accounting for maternal origin.

Methods

National Study of HIV in Pregnancy and Childhood (NSHPC)

Pregnancies in women living with HIV resulting in a live birth or stillbirth at ≥24 week gestation in 2007-2015 and reported to the UK and Ireland's NSHPC by March 2017 were included in this study. The NSHPC is a comprehensive, population-based surveillance study through which data are collected on pregnancies in women diagnosed with HIV and their children seen for care in the UK and Ireland. All pregnancies are notified prospectively by a named respondent in each maternity unit through an active, quarterly surveillance scheme. Data are collected on demographic, clinical and pregnancy characteristics, including pregnancy complications and outcomes, using study reporting forms. Maternal origin is self-reported. Full methodological details have been described elsewhere[10,12].

Definitions and classifications

In the UK the definition of a stillborn infant is an infant born "after the 24th week of pregnancy and which did not at any time breathe or show any other signs of life" (Still-Birth (Definition) Act 1992). Respondents report when a notified pregnancy ends in stillbirth, but data are not routinely collected on the circumstances or timing (i.e. in utero or intrapartum). Gestational age at delivery was reported in completed weeks. Preterm deliveries were defined as those before 37 completed weeks gestation and small for gestational age as $<10^{th}$ percentile. Maternal age at delivery was grouped into quartiles based on the distribution of maternal age. We defined a 'baseline' CD4 count as the earliest reported measurement between eight weeks before conception and one week after delivery and categorised CD4 count as $\leq$350 cells/mm^3 and >350 cells/mm^3. Conception was estimated as occurring 2 weeks after the date of last menstrual period. We defined a report of "pre-eclampsia" (of any severity) as pre-eclampsia, pregnancy-induced hypertension (PIH) with proteinuria or haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome. We defined "diabetes" as gestational diabetes or pre-existing diabetes. We used the convention of 'XTC' (meaning either emtricitabine [FTC] or lamivudine [3TC]) in reporting antenatal ART regimens.

Risk factors analysis

We analysed the effects of risk factors on stillbirth by fitting a Poisson regression model with robust standard errors[13] to account for repeated pregnancies in the same mother. The model included stillbirth risk factors reported in the literature and collected in the NSHPC: calendar year, maternal age at delivery, parity, timing of antenatal care, region of origin, pre-eclampsia, diabetes, baseline CD4 count in pregnancy and ART at conception. As there were over 20% of missing data for antenatal booking, pre-eclampsia and diabetes, and around 10% for parity and

CD4 count (Supplementary Material 1, http://links.lww.com/QAI/B332. Frequency and percentage of missing values per variable) multiple imputation with chained equations (MICE) was used to deal with missing data based on the assumption that the data were missing at random (MAR)[17,14]. We imputed missing data for our covariates (maternal origin, timing of first antenatal appointment, parity, CD4 count, pre-eclampsia, diabetes and ART at conception) using calendar year, country of delivery within UK/Ireland, maternal age, history of injecting drug use, gestational age and birth outcome (live/stillbirth). We generated 20 imputed datasets and combined regression coefficients' estimates across these using Rubin's rule[15]. We tested whether missingness was completely at random (MCAR) rather than MAR by examining differences in the pattern of missingness and assessed the MAR model performance by comparing the model estimates with the unadjusted analysis estimates.
Risk factors analysis was conducted among singletons. Results were considered statistically significant at the 0.05 level. Differences in proportions were tested for statistical significance using chi-squared tests. Statistical analyses were performed using Stata version 13.1 (StataCorp, College Station, TX, USA).

Comparison of NSHPC data on women with HIV to national data on the general population

National stillbirth rates by maternal origin were derived from the annual national birth statistics published by the UK Office for National Statistics (ONS)[16], which covers all births registered in England and Wales. The statistics are derived from information recorded when births and deaths are registered in England and Wales, which is a legal requirement. Data for maternal origin did not distinguish between single and multiple births. Consequently, the NSHPC comparison data included both singleton and multiple births delivered in England and Wales. We adopted the geographically-based grouping of countries of the ONS National Statistics Country Classification (NSCC)[17] to group maternal origin as follows: (1) UK/Ireland – the

baseline, (2) Western Europe and Other Western Countries/Eastern Europe (WEWC/EE), (3) East Africa, (4) Southern Africa, (5) Rest of Africa (Western, Central and North Africa), (6) Caribbean/Latin America and (7) Asia. ONS and NSHPC stillbirth rates were compared within each maternal region of birth group by calculating standardised stillbirth ratios (stillbirth rate in NSHPC/stillbirth rate in ONS). We calculated the total number of stillbirths that would be expected in the NSHPC if maternal-origin specific stillbirth rates were the same as in the general population, by multiplying the ONS stillbirth rate within each maternal origin group by the number (in 1000s) of women in that maternal origin group in the NSHPC. Finally, we calculated the overall standardised stillbirth ratio (total observed stillbirths/total expected stillbirths in the NSHPC □□100), and computed the 95% confidence interval (CI) for standardised ratios using Wald approximation[18].

Results

Deliveries to women living with HIV, 2007-2015

A total of 10434 singleton deliveries in 8090 women with HIV were reported to the NSHPC, of which 89% (9275) occurred in England and Wales. Most pregnancies were in women of African origin (7781/10317, 75.4%) with East Africa being the most common region of origin (4319/10317, 41.9%); 48.6% (5023/10328) of pregnancies were conceived on ART, and in 34.4% (3381/9830) of pregnancies, baseline CD4 count was ≤350 cells/mm^3. Most pregnancies were in women who were parous (7221/9926, 72.8%), and the median age was 32.7 years (IQR 28.6-36.4) at delivery.

Stillbirths among women living with HIV

Eighty-nine singletons were stillborn, equivalent to a rate of 8.5 (95% CI 6.9, 10.5) per 1,000 births (Table 1). Over the study period the stillbirth rate tended to decline (Table 1) but the temporal trend was not statistically significant (*p*-value for trend=0.14). As expected most stillbirths were delivered preterm (65/89 [73.0%] compared with 1105/10345 [10.7%] among live births), more than half at <34 weeks (46/89 [51.7%] compared with 410/10345 [4.0%] of livebirths); 58.2% (39/67) of stillborn infants were male, and 50.0% (31/62) were small for gestational age. Congenital anomalies were reported in 16.1% (10/62) of stillborn infants compared with 2.9% (286/10026) of live born infants.

We identified the nine most frequent antenatal ART regimens (Figure 1), all used in at least 3% of pregnancies. Ritonavir-boosted lopinavir (LPV/r) with 3TC/zidovudine (ZDV) was the most common regimen, received in 24.5% (2483/ 10153) of pregnancies, mainly earlier in the study period (1517/2484, 61.1% in 2007-2009). The second most frequent regimen (886/10153, 8.7%) was atazanavir (ATV)+XTC/tenofovir (TDF) followed by efavirenz (EFV)+XTC/TDF (862/10153, 8.5%). The highest stillbirth rate was among pregnancies in women on nevirapine (NVP)+XTC/TDF, at 14.3 per 1000 births (95% CI 5.3, 31.2), followed by LPV/r+3TC/ZDV at 11.7 per 1000 births (95% CI 7.8, 16.8) (Figure 1). Pregnancies in women on other NVP-based regimens had lower stillbirth rates: 8.3 (95% CI 2.3, 21.2) for NVP+XTC/abacavir (ABC) and 6.0 per 1000 (95% CI 1.2, 17.7) for NVP+XTC/ZDV but the differences were not statistically significant (Supplementary Material 2, http://links.lww.com/QAI/B332. Stillbirths by ART regimens). We did not perform any adjusted analysis by ART regimens because of the relatively small sample size by ART regimens.

Risk factors for stillbirth among women with HIV

Pregnancies resulting in a stillbirth were more likely to occur in women born in Asia, East Africa and the rest of Africa (excluding Southern Africa), or with a baseline CD4 count <350 cells/mm^3, and in those who were primiparous, of older age or suffered from pre-eclampsia or diabetes. These risk factors (except for African maternal origin) remained statistically significant in the multivariable regression model (Table 2). The model suggested that pre-eclampsia increases the risk of delivering a stillborn by over 8-fold (OR 8.28, 95% CI 4.44, 15.5) and maternal Asian origin by 4-fold. Conceiving on ART was not associated with an increased risk. The distributions of missingness in the data for parity, baseline CD4 count, pre-eclampsia, and diabetes varied significantly across stillbirths (Supplementary Material 1, http://links.lww.com/QAI/B332) providing evidence against MCAR. An unadjusted analysis including only complete cases (*n*=6567) implied a good performance of the multiple imputation model, with no substantial difference between the estimates from it and those from the estimates obtained with MICE.

Comparison of stillbirth rates in NSHPC with the general population, by maternal origin

Table 3 presents stillbirth rates between 2007 and 2015 in England and Wales for the general population (ONS data) and for the NSHPC, by maternal origin. The overall crude stillbirth rate was

5.2 per 1000 for the general population compared with 8.6 per 1000 for women living with HIV. The highest crude rates were seen in women born in East Africa and the rest of Africa (excluding Southern Africa) in the general population and in women born in Asia and East Africa in the NSHPC population. The standardised stillbirth ratio (with the general population as the reference

population) was 129 (95% CI 101, 165). In other words, after taking into account maternal origin the stillbirth rate in women with HIV remained 29% higher than the stillbirth rate in the general population (Table 3).

Discussion

Between 2007 and 2015 in the UK and Ireland the rate of stillbirth was 8.5 (95% CI 6.9, 10.5) per 1000 in women with HIV, of whom two-thirds had CD4 counts above 350 cells/mm^3 and half were on ART at conception. Risk factors associated with increased stillbirth risk in women with HIV were pre- eclampsia, diabetes, a CD4 count <350 cells/mm^3, older age, primiparity and maternal Asian origin. Conceiving on ART was not associated with stillbirth. There was a non-significant trend of declining stillbirths over the study period.

The finding that women with low CD4 count had an increased stillbirth risk (adjusted IRR 1.69, 95%CI 1.09, 2.63) is consistent with previous findings showing that poor maternal immune status is associated with increased risk of stillbirth[19-21] and miscarriage[20,22], with symptomatic HIV disease also a risk factor[22]. Immunological status of pregnant women living with HIV in the UK and Ireland has improved over time, reflecting the increasing proportion already on ART at conception[11]. However, among the small proportion of women diagnosed with HIV for the first time in pregnancy (10% in 2016) half had a CD4 count <350 cells/mm^3 in 2012-2016[23], suggesting that this group may be at high risk for adverse pregnancy outcomes. Furthermore, many of these women are migrants who may experience barriers to accessing HIV services[24] and antenatal care[25,26].

A few recent studies have addressed the association between stillbirth and specific ART regimens, or timing of ART initiation[2-4,19,27]. Uthman et al included two studies (from France and Botswana) with stillbirth as an outcome in their meta-analysis, reporting a risk ratio of 1.30 (95% CI 0.99-1.69) for women starting ART pre-conception versus antenatally[2]. We observed no increased stillbirth risk in women starting ART pre-conception (IRR 0.76 [95% CI 0.50, 1.16]). In a Botswana study of pregnancies in 2014-2016 with around half exposed to ART from conception, NVP+ZDV/3TC was associated with an adjusted relative risk (ARR) of stillbirth of 2.31 (95%CI 1.64, 3.26) versus EFV+TDF/3TC[4]. In our study, stillbirth rates in women on NVP-based regimens varied by backbone, from 14.3 (95%CI 5.3, 31.2) per 1000 for NVP+XTC/TDF to 6.1 (95%CI 1.3, 17.7) per 1000 for NVP+XTC/ZDV, a rate slightly lower than for EFV+XTC/TDF (7.0, 95%CI 2.6, 21.3). We were unable to conduct a regimen-specific adjusted analysis, and confounding by indication may be important given that guidelines do not recommend starting NVP-containing regimens in pregnancy when CD4 counts are >250 cells/mm^3. Although the stillbirth rate for LPV/r+3TC/ZDV was the second highest rate, at 11.7 (95%CI 7.8, 16.8) per 1000, this was not significantly different from other regimens; similarly in the Promoting Maternal-Infant Survival Everywhere (PROMISE) trial there was no significant difference in stillbirth rates across the ZDV only, LPV/r+3TC/ZDV and LPV/r+TDF/FTC arms[28]. Although LPV/r+3TC/ZDV was the most common regimen in our study, its use declined substantially over the study period[29].

Pre-eclampsia was associated with an eight-fold increased risk of stillbirth in our study, consistent with what is known regarding risks of hypertensive diseases of pregnancy[30]. Around 3% of women were in this high risk group, a similar proportion to a South African study of pregnant women with HIV[31] and this is also within the range expected for the

general UK antenatal population[32]. The increased risk of stillbirth in older women is consistent with our previous report of a nearly 2.5-fold increased risk in women over 40 years compared with younger women[33]. By 2010-2014, nearly one in ten pregnancies in the NSHPC were in women aged 40 or older, and this is a risk group that is likely to grow in the future.

Our NSHPC analyses indicated that among women living with HIV, there was a higher stillbirth rate in some migrant groups than among women born in the UK/Ireland, and this reached statistical significance among women born in Asia who remained at over a four-fold (OR 4.8, 95%CI 1.5, 15.4) increased risk of stillbirth in adjusted analyses. This pattern is reflected in the general population, with ONS data showing a stillbirth rate of 6.8/1000 for women born in Asia vs 4.7/1000 for women born in UK/Ireland. Studies in the general population which have focused on South Asian women (who account for the most births to women of Asian origin in the UK) have suggested a range of possible factors involved in this elevated risk; these include perinatal mortality risk increasing at an earlier gestation among South Asian than white women and being associated with low birthweight [34], and obesity interacting with South Asian maternal origin to elevate stillbirth risk [35]. In our study, the association between Asian origin and stillbirth risk remained after adjusting for pre-eclampsia, diabetes, timing of antenatal care initiation and other factors; other infections (maternal syphilis, congenital cytomegalovirus infection) were reported in two of the six stillbirths in this group (data not shown), and may have contributed to stillbirth risk.

In addition to the analyses conducted based only on NSHPC data, we carried out an analysis to increase our understanding of how the stillbirth rates within maternal origin groups among women living with HIV compared to those among the general population, using national

registration data. The crude stillbirth rate in 2007-2015 was 8.6 per 1000 in women with HIV and 5.2 per 1000 in the general population of women delivering in England and Wales. After accounting for the higher stillbirth rates in women from different migrant groups through standardisation, we showed that the rate of stillbirth in women with HIV was 29% (SSR 129, 95%CI 100.0, 165.3) higher than the general population. This analysis only accounts for maternal origin and not for other factors associated with increased risk of stillbirth, such as pre-eclampsia.

This study is one of the few addressing stillbirth in women with HIV delivering in high income countries. Most studies on stillbirth and maternal HIV have been conducted in low- and middle- income countries (LMICs) where overall stillbirth rates are generally higher than in high income countries[6], making comparisons difficult. Two studies in high income countries have reported stillbirth rates in women living with HIV: in the French Perinatal Cohort 0.8% of pregnancies ended in stillbirth between 2000 and 2011[36], a rate similar to that reported here. A low stillbirth rate of 0.4% was also reported in the Pediatric AIDS Clinical Trials Group (PACTG) 316 trial (1997-2000), which evaluated adding single-dose NVP to background ART (mainly in the United States and France), reflecting the selected study population[37]. Nonetheless, the Women Interagency HIV Study in the United States reported a stillbirth rate of 2.6% among 461 women with ≥1 viral load in the year preceding delivery (1994 to 2013)[38]. Among studies in LMICs, one of the largest and most recent was conducted in Botswana, and reported a 2.3% stillbirth rate among nearly 6,500 women initiating ART in pregnancy[27].

Early identification and appropriate management of risk factors for stillbirth through antenatal and intrapartum care has been shown to reduce the number of stillbirths in the UK. "Each Baby Counts" is a national quality improvement programme established in 2015 by the Royal College of Obstetricians and Gynaecologists that aims to halve the incidence of stillbirths, neonatal death and severe brain injury as a result of incidents during term labour[39]. In our study, three-quarters of the stillborn infants were preterm. Global figures of the proportion of stillbirths that are preterm are difficult to find, as stillbirths are usually not reported by gestational age; however, a recent study from a World Health Organization survey in LMICs estimated that at least half of stillbirths were preterm[40]. We also showed that substantially more stillborn than live-born infants had congenital abnormalities (16% versus 3%). These findings highlight that pharmacovigilance studies, particularly birth defect surveillance, should include stillbirths and live births to avoid missing important outcomes. Potential associations between maternal HIV disease, ART, preterm delivery and other adverse birth outcomes are complex, and mechanisms remain poorly understood[2-4,28,41-43]. More research is needed to understand the circumstances around stillbirth in women living with HIV, in order to identify specific interventions. To this end, the NSHPC team plans to undertake an audit of pregnancies ending in stillbirth, following established methodology used in an ongoing audit of perinatal HIV transmission[44].

The key strength of our study is the size and comprehensive national coverage of the NSHPC which allowed us to investigate stillbirth rates associated with a number of different variables. Comparison of the NSHPC and ONS data enabled calculation of standardised stillbirth ratios; limitations of this analysis were that the NSHPC births are included in the ONS data (however, these represent only 0.2% of stillbirths and 0.15% of births) and that the analysis included singletons and multiple births. Our study was limited by the nature of the

surveillance data collected, which did not include details on timing of fetal death (antepartum or intrapartum), nor on maternal smoking or obesity. We found that Asian-born women in the NSHPC had a very high risk of stillbirth but were unable to determine the reasons partly due to the small number of women in this group, which affected the precision of the estimates in the multivariable analysis. Although we successfully accounted for missing data in our analysis using multiple imputation, we could not be certain that the assumption of MAR held for all variables. However, results based on imputed and complete case analysis were similar.

Between 2007 and 2015 the stillbirth rate in women with HIV infection delivering in the UK and Ireland was 8.5 per 1000, compared with 11.0 per 1000 in 2000-2006[10]. We showed that the SSR for stillbirth was 129, taking into account maternal origin. The minority of women with low CD4 counts may be at increased stillbirth risk, underscoring the importance of strategies to promote earlier HIV testing (i.e. before pregnancy). A key goal of both antenatal care and HIV management in pregnancy are to optimise maternal, fetal and infant health. The important successes in preventing new perinatal infections evidenced by the current low vertical transmission rate of 0.3%[11] highlight the need to focus attention on achieving a better understanding of stillbirth risk in this population, and identifying which interventions might be effective in reducing this risk.

Ethics

The NSHPC has received ethical approval from the London Multi-Centre Research Ethics Committee (MREC/04/2/009).

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Table 1. Crude stillbirth rates per 1000 births in women with HIV by risk factors

		Stillbirth/Total births	Crude stillbirth rate (95% CI) per 1000 births	*p*-value*
		89/10,434	8.5 (6.9, 10.5)	
Year of delivery				0.14
	2007-2009	41/3,872	10.6 (7.6, 14.4)	
	2010-2012	30/3,624	8.3 (5.6, 11.8)	
	2013-2015	18/2,938	6.1 (3.6, 9.7)	
Country of delivery				0.098
	England & Wales	84/9,275	9.1 (7.2, 11.2)	
	Other**	5/1,159	4.3 (1.4, 10.1)	
Maternal age at delivery				0.32
n=10434	<28 years	12/2,253	5.3 (2.8, 9.3)	
	28-32 years	23/2,499	9.2 (5.8, 13.8)	
	33-36 years	27/2,858	9.4 (6.2, 13.7)	
	>36 years	27/2,824	9.6 (6.3, 13.9)	
Maternal origin				0.055
n=10317	UK/Ireland	7/1,494	4.7 (1.9, 9.7)	
	WEWC/EE	2/516	3.9 (0.5, 14.0)	
	East Africa	43/4,319	10.0 (7.2, 13.4)	
	Southern Africa	4/664	6.0 (1.6, 15.4)	
	Rest of Africa	25/2,798	8.9 (5.8, 13.2)	
	Caribbean/LA	1/259	3.9 (0.5, 14.0)	
	Asia	6/267	22.5 (8.2, 48.9)	
Timing of first antenatal appointment (weeks)				0.099
n=8161	<12	52/6,526	8.0 (6.0, 10.4)	
	≥12	19/1,629	11.7 (6.7, 13.1)	
Parity (at delivery)				0.039
n=9926	Primiparous	30/2,705	11.1 (7.5, 15.8)	
	Multiparous	50/7,221	6.9 (5.1, 9.1)	
History of intravenous drug use				
	No	88/10,180	8.6 (6.9, 10.7)	0.72
	Yes	1/165	6.0 (1.5, 33.8)	
Baseline CD4 count (cell/mm^3)				0.001
n=9381	>350	38/6,449	5.9 (4.2, 8.1)	
	≤350	41/3,381	12.1 (8.7, 16.5)	
Pre-eclampsia				<0.001
n=9466	No	52/9,213	5.8 (4.3, 7.5)	
	Yes	12/253	47.4 (24.5, 82.9)	
Diabetes				0.004
n=9466	No	59/9,178	6.4 (4.9, 8.3)	
	Yes	6/288	20.8 (7.6, 45.3)	
ART at conception				0.28
n=10328	No	53/5,305	10.0 (7.5, 13.1)	
	Yes	36/5,023	7.2 (5.0, 9.9)	

WEWC/EE, Western Europe (UK/Ireland excluded) and other Western Countries (Canada and United States)/ Eastern Europe; LA, Latin America. CI, confidence interval.
* ***p***-value for chi-squared test; ** includes Scotland, Republic of Ireland, Northern Ireland and Channel Islands.

Table 2. . Risk factor analyses for stillbirth among women with HIV

		Livebirths	Stillbirths	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI) for imputed datasets
		n=10345	*n*=89		
		n (%)	*n* (%)		
Year of delivery *n=10434*					
	2007-2009	3831 (37.0)	41 (46.1)	1.00	1.00
	2010-2012	3594 (34.7)	30 (33.7)	0.78 (0.49, 1.24)	0.77 (0.47, 1.25)
	2013-2015	2920 (28.2)	18 (20.2)	0.58 (0.33, 1.03)	0.57 (0.32, 1.01)
Maternal age at delivery *n=10434*					
	Per one year increase			1.04 (1.00, 1.09)	1.07 (1.00, 1.15)
Maternal origin *n=10317*					
	UK/Ireland	1487 (14.5)	7 (8.0)	1.00	1.00
	WEWC/EE	514 (5.0)	2 (2.3)	0.83 (0.17, 3.96)	0.86 (0.20, 3.63)
	East Africa	4276 (41.8)	43 (48.9)	2.12 (0.95, 4.73)	1.62 (0.75, 3.51)
	Southern Africa	660 (6.5)	4 (4.5)	1.29 (0.38, 4.37)	0.98 (0.29, 3.25)
	Rest of Africa	2773 (27.1)	25 (28.4)	1.91 (0.83, 4.39)	1.30 (0.56, 3.02)
	Caribbean/LA	258 (2.5)	1 (1.1)	0.82 (0.10, 6.63)	0.70 (0.09, 5.56)
	Asia	261 (2.6)	6 (6.8)	4.80 (1.49, 15.4)	4.00 (1.39, 11.5)
First antenatal appointment (gestation weeks) *n=8089*					
	<12	6474 (80.0)	52 (72.2)	1.00	1.00
	≥12	1615 (20.0)	20 (27.8)	1.46 (0.86, 2.49)	1.49 (0.86, 2.59)
Parity (at delivery) *n=9926*					
	Primiparous	2675 (27.2)	30 (37.5)	1.60 (1.01, 2.54)	1.73 (1.11, 2.69)
	Multiparous	7171 (72.8)	50 (62.5)	1.00	1.00
Baseline CD4 count (cells/mm^3) *n=9381*					
	≤350	3340 (34.2)	41 (51.9)	2.06 (1.32, 3.21)	1.69 (1.09, 2.63)
	>350	6411 (65.8)	38 (48.1)	1.00	1.00
Pre-eclampsia *n=9466*					
	No	9160 (97.4)	53 (81.5)	1.00	1.00
	Yes	241 (2.6)	12 (8.5)	8.24 (4.27, 15.9)	8.28 (4.44, 15.5)
Diabetes *n=9466*					
	No	9119 (97.0)	59 (90.8)	1.00	1.00
	Yes	282 (3.0)	6 (9.2)	3.24 (1.42, 7.38)	2.76 (1.05, 7.23)
ART at conception *n=10328*					
	No	5252 (51.3)	53 (59.5)	1.00	1.00
	Yes	4987 (48.7)	36 (40.5)	0.72 (0.47, 1.10)	0.76 (0.50, 1.16)

Table 3. Comparison with stillbirth rate by maternal origin in the general population

	ONS data (general population England and Wales)				NSHPC data (women with HIV, England and Wales)				
	Births (N)	**SB (N)**	**Crude SB rate/ 1000 births**		**Births (N)**	**SB (N)**	**Crude SB rate/ 1,000 births**	**Expected SB † (N)**	**SSR‡**
Overall*	6536277	33859	5.2		9526	82	8.6	63.5	129.2 (100.9, 165.3)
Maternal origin									
UK/Ireland	4286007	20058	4.7		1284	6	4.7	6.0	99.85
WEWC/EE	755549	3523	4.7		433	2	4.6	2.0	99.12
East Africa	89823	636	7.1		4227	42	9.9	29.9	140.34
Southern Africa	35796	160	4.5		508	2	3.9	2.3	88.08
Rest of Africa	285015	2221	7.8		2596	23	8.9	20.2	113.73
Caribbean	82290	487	5.9		230	1	4.4	1.4	73.44
Asia	1001797	6774	6.8		248	6	24.2	1.7	357.36
Other/unknown	1755417	10728	6.1		158	3	19.0	**	**

SB, stillbirth; ONS, UK Office for National Statistics; NSHPC, UK and Ireland's National Study of HIV in Pregnancy and Childhood; SSR, Standardised Stillbirth Ratio

*Includes only births with available data for maternal origin; maternal origin was other/missing for 1,755,417 (21.2%) births in ONS.

†Using ONS as reference population

‡Standardised by maternal region of origin (number of observed stillbirths / number of expected stillbirths x 100)

**Comparison between ONS and NSHPC not interpretable as the underlying composition of "other/unknown" in the two populations may differ.