Maternal HIV infection associated with small-for-gestational age infants but not preterm births: evidence from rural South Africa

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BACKGROUND: Human immunodeficiency virus (HIV) is prevalent in many countries where small-for-gestational age (SGA) and premature delivery are also common. However, the associations between maternal HIV, preterm delivery and SGA infants remain unclear. We estimate the prevalence of SGA and preterm (<37 weeks) births, their associations with antenatal maternal HIV infection and their contribution to infant mortality, in a high HIV prevalent, rural area in South Africa.

METHODS: Data were collected, in a non-randomized intervention cohort study, on all women attending antenatal clinics (2001–2004), before the availability of antiretroviral treatment. Newborns were weighed and gestational age was determined (based on last menstrual period plus midwife assessment antenatally). Poisson regression with robust variance assessed risk factors for preterm and SGA birth, while Cox regression assessed infant mortality and associated factors.

RESULTS: Of 2368 live born singletons, 16.6% were SGA and 21.4% were preterm. HIV-infected women (*n* = 1189) more commonly had SGA infants than uninfected women (18.1 versus 15.1%; *P* = 0.051), but percentages preterm were similar (21.8 versus 20.9%; *P* = 0.621). After adjustment for water source, delivery place, parity and maternal height, the SGA risk in HIV-infected women was higher [adjusted relative risk (aRR) 1.28, 95% confidence interval (CI): 1.06–1.53], but the association between maternal HIV infection and preterm delivery remained weak and not significant (aRR: 1.07, 95% CI: 0.91–1.26). In multivariable analyses, mortality under 1 year of age was significantly higher in SGA and severely SGA than in appropriate-for-gestational-age infants [adjusted hazard ratio (aHR): 2.12, 95% CI: 1.18–3.81 and 2.77, 95% CI: 1.56–4.91], but no difference in infant mortality was observed between the preterm and term infants (aHR: 1.18 95% CI: 0.79–1.79 for 34–36 weeks and 1.31, 95% CI: 0.58–2.94 for <34 weeks).

CONCLUSIONS: Maternal HIV infection increases the risk of SGA, but not preterm births, in this cohort.

Key words: HIV / SGA / preterm / Africa / low birthweight

Introduction

Low birthweight (LBW) is a significant risk factor for infant mortality (Bhutta *et al.*, 2005). LBW is commonly defined at a cut-off of 2500 g, and may be due to preterm delivery, growth restriction or both (Euser *et al.*, 2008). In developed countries, LBW rates are low and caused mainly by prematurity while in developing countries, where the prevalence of LBW is >10% (Costello *et al.*, 2001),

LBW is often due to intrauterine growth restriction (IUGR) and often associated with small-for-gestational age (SGA) (Villar and Belizan, 1982; Kramer, 1987a,b). Prematurity SGA have heterogeneous etiologies (Rayco-Solon *et al.*, 2005), and different outcomes for the infant (Verhoeff *et al.*, 2001; Zeitlin *et al.*, 2001; Rayco-Solon *et al.*, 2005); SGA infants have poorer outcomes than appropriate-for-gestational age (AGA) infants, especially if they are preterm (Zeitlin *et al.*, 2001). SGA is based on the percentile of the

birthweight-for-gestational age and was not used to indicate IUGR in our study. Factors associated with SGA and preterm delivery include socio-economic status, short maternal stature and low parity (Kramer, 1987a,b; Verhoeff et al., 2001; Zeitlin et al., 2001). In developing country settings, it is important to understand factors associated with preterm births and SGA and their contribution to infant mortality, so that limited resources can be directed at those most at risk and so that the Millennium Development goal 4 aimed at reducing under-5 mortality by two-thirds between 1990 and 2015, can be achieved.

Human immunodeficiency virus (HIV) is highly prevalent in many of the countries where SGA and premature delivery are also common, and maternal HIV has been associated with adverse pregnancy outcomes such as spontaneous abortions, LBW and stillbirths (Langston et al., 1995; Rollins et al., 2007). However, the detail of associations between maternal HIV, preterm delivery and SGA infants remains unclear. In high HIV prevalence areas, some studies have reported a 70% increased risk of preterm delivery and a 40% increased risk of SGA associated with HIV (Bulterys et al., 1994; Taha et al., 1995), but this is not confirmed in other studies (Temmerman et al., 1994; Verhoeff et al., 2001). These inconsistent findings may be due to the lack of a standardized definition of SGA, difficulty in assessing gestational age or not adjusting for confounding factors (Brocklehurst and French, 1998; Verhoeff et al., 2001). The inability to obtain precise information on pregnancy duration in resource-limited settings has resulted in the use of birthweight as a proxy for gestational age in some studies (Temmerman et al., 1990; Taha et al., 1995). However, although birthweights are routinely recorded in health facilities, these are often not recorded in settings where a substantial number of births occur at home.

In this study, we estimate the prevalence of SGA and preterm births in a HIV prevalent, rural area in South Africa and evaluate the effect of maternal HIV infection on the risk of SGA or preterm births; we further quantify the contribution of SGA and preterm birth to infant mortality.

Materials and Methods

This vertical transmission study (VTS) enrolled HIV-infected and -uninfected pregnant women in nine antenatal clinics in two sites, the largest in rural Umkhanyakude district, northern KwaZulu-Natal and the other outside Durban, South Africa (Coovadia et al., 2007; Bland et al., 2010). Recruitment was from August 2001 to September 2004 with mothers and children followed for 2 years post-natally. Initially, all HIV-infected women and a systematic sample of uninfected women were enrolled in the study. However from July 2003, all women attending antenatal visits were offered enrolment before HIV testing. All pregnant women were tested for HIV and counselled at the antenatal clinic, by lay HIV counsellors, on infant feeding options according to the World Health Organization (WHO)/United Nations programme on AIDS recommendations current at that time (Bland et al., 2007). All HIV-infected women and their infants were offered single-dose nevirapine, but at the time of the study, antiretroviral treatment was not available through the public health services in South Africa. The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

Gestational age at delivery was determined on the basis of last menstrual period (collected at antenatal visits by trained study staff), unless adjusted by midwife assessment on the basis of a clinical assessment.

Birthweight was measured by study staff or taken from clinic registers within 72 h of birth. For infants born at home, mothers brought their infant to the clinic the following day (or within 72 h) for immunization (BCG and polio), weighing and registration to obtain a road-to-health card (RTHC); this is the general practice in South Africa since without the RTHC, children cannot access public services such as clinics or school. These infants were weighed by the study staff. However, if women delivered in facilities outside the study area or study staff were not available, we used the weight documented by the Department of Health staff on the RTHC (Rollins et al., 2007).

Infants attended monthly clinic visits with a study nurse, scheduled from 6 weeks to 9 months of age, and thereafter quarterly to 24 months. All study clinic assistants who carried out anthropometric measurements at each visit received standardized anthropometry instructions with regular in-service training also given to ensure strict adherence to the techniques. The clinic manager conducted quality assurance checks of measurement techniques throughout the study. The same measuring equipment was used at all of the clinics with precision within 10 g for newborns while for older children, portable electronic weighing scales with taring capability and a precision to 100 g (UNICEF electronic scale 890) was used as recommended by WHO (de Onis et al., 2004). At approximately weekly intervals, the clinic manager checked calibration using standard metal weights. Further, each child had two weights recorded and if their difference was >100 g, a third measurement was taken and the two weights within 100 g were recorded; the mean value was calculated for this analysis (de Onis et al., 2004).

Dried blood spot (DBS) samples were collected from all HIV-exposed newborn infants within 72 h of birth, and then at each scheduled clinic visit to determine their HIV status. HIV status was established by quantitative HIV RNA assay with a sensitivity of 80 copies/ml (equivalent to 1600 copies per 50 μl DBS) (Bland et al., 2010). Infants were considered to be perinatally infected if the DBS sample taken at 4−8 weeks was positive, post-natally infected if the 4−8-week sample was negative and any subsequent sample was positive or infected with 'timing unknown' if the first sample was taken after 8 weeks and was positive.

In the antenatal period, socio-demographic and past and current pregnancy data were collected using structured questionnaires; post-natally, daily infant morbidity and feeding practices were documented at weekly intervals, and maternal weights, mid-upper arm circumference (MUAC) and height were measured (Bland et al., 2010). For these analyses, the weight and MUAC taken at 6 weeks post-delivery were used.

Definitions

Antenatal maternal HIV status was classified into HIV positive and negative; maternal CD4 count was measured in all HIV-positive women. LBW was defined as <2500 g (Kramer, 1987a,b). Infants were classified as preterm if the gestational age at birth was <37 completed weeks, and as SGA if below the 10th percentile of the birthweight-for-gestational age, as recommended by the WHO (WHO, 1995), with the US population-based reference used as the standard for comparability of the prevalence rates of SGA, and the potential effect of maternal HIV infection on SGA, with previous studies elsewhere in Africa (Alexander et al., 1996). To assess severely small-for-gestational-age infants, risk associations were further analyzed at a 3% cutoff (Oken et al., 2003). Size for gestational age was therefore categorized into three groups based on percentiles: AGA, ≥10%; SGA, 3 ≤ 10% and <3%, severely SGA. We only included singleton live births, given the increased risk of LBW and premature delivery for multiple birth; we also excluded stillbirths as four-fifths had missing birthweights. Place of delivery was classified into health facility and home. Parity was classified so as to compare primiparae with multiparae (Mansour et al., 2002) and was categorized as 0, 1−3 or ≥4. Based

on the maternal enrollment clinic, residential area was classified as rural, peri-urban or urban, as most people in this setting are likely to attend their nearest clinic, with the median travel time of 81 min (Tanser, 2006). Neonatal mortality was defined as a death in the first 4 weeks of life (Lawn et al., 2005), while infant mortality was defined as the death by 12 months of age.

Statistical analysis

Data were analysed using Stata Version 11.2 (STATA Corps, College Station, TX, USA). Differences between HIV-infected and -uninfected women were assessed using t-test for continuous variables with normal distribution, χ^2 test for categorical variables and Fisher's exact test if the numbers were small. Poisson regression, with a value of one attributed to each participant's follow-up time to obtain prevalence ratio estimates (done on all subjects and then separately among the HIV-positive and HIV-negative mothers), was used to assess factors associated with SGA and preterm delivery. To minimize overestimation of the relative risk when using Poisson regression for a categorical covariate of interest, a robust variance procedure was used (Lin and Wei, 1989). This method was considered to be a better alternative than the logistic regression for analysis of cross-sectional data, with the latter producing higher estimates than the former (Coutinho et al., 2008). For ease of comparison with other studies, we repeated our analyses using the conventional binary logistic regression and found essentially similar results to those presented here using Poisson regression. Variables were considered for inclusion in the multivariable model. Goodness-of-fit tests, assessed using the likelihood-based Akaike information criteria (AIC), were used to determine the variables that significantly improved the final Poisson models' fit (Bruin, 2006).

Mortality by maternal HIV status and SGA was assessed using Kaplan–Meier survival analysis. Follow-up time was computed as time from birth to withdrawal, loss to follow-up, migration or death if before the first year of life, whichever came first, allowing for child's HIV status as a time-varying

variable for infant mortality analyses. Risk factors for infant mortality were assessed in univariable and multivariable Cox regression models with child HIV infection as a time-dependent variable; for the adjusted model, variables with a statistically significant association univariately were included in addition to three included (parity, maternal age and education) a priori (Ndirangu et al., 2010).

Results

There were 2811 live births in the cohort; 350 live births were excluded from the analysis: 76 (2.7%) had improbably high gestational age, 2 (0.1%) were missing birthweight and gestational age, 9 (0.3%) were missing gestational age only, 187 (6.7%) were missing birthweight data only and 76 (2.7%) had an improbable birthweight/gestational age combination (Fig. 1). A further 93 (3.3%) live births were excluded either because they were multiple births (86) or due to indeterminate maternal antenatal HIV status (7). A total of 2368 live born infants (1189 of HIV-infected and 1179 of HIV-uninfected women) were thus included in the analyses. HIV-uninfected women were significantly younger than infected women, more likely to be enrolled from rural clinics and less likely to have infants with LBW and SGA (Table I). HIV-infected women did not differ significantly from uninfected women with respect to place or type of delivery, gestational age or water source.

Prevalence of SGA and preterm deliveries

The median birthweight was 3100 g (inter-quartile range: 2850–3400) and 198 (8.4%) infants were LBW. Overall, 506 (21.4%) infants were born preterm, of these 188 (37%) were born at 36 weeks and nearly one-third were <34 weeks gestational age and 36 (7.1%) preterm
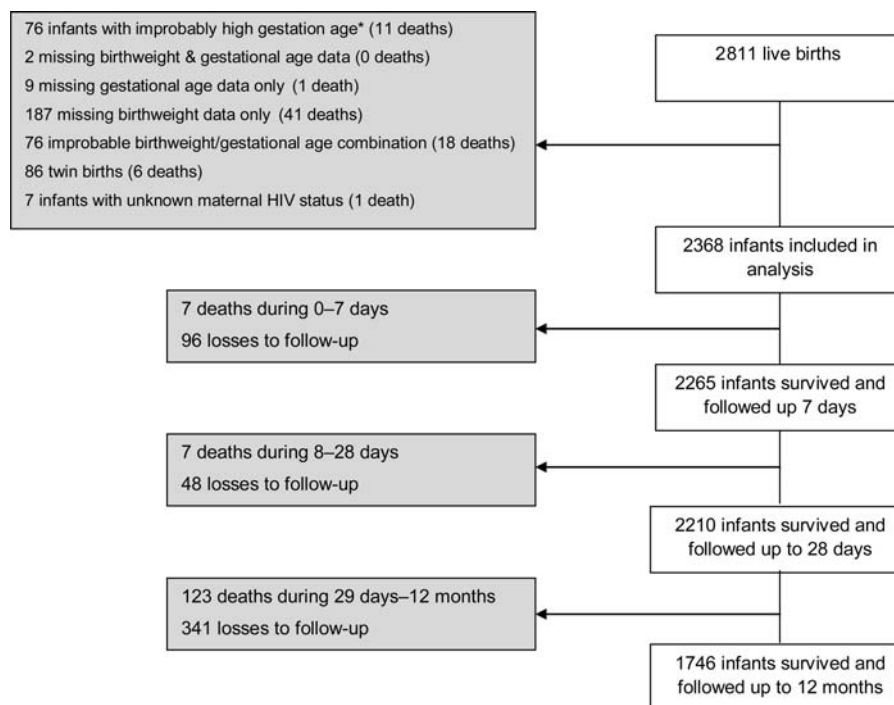
Figure 1 Study population. *Improbably high gestational age was >46 weeks.

Table I Maternal and infant characteristics by maternal HIV status.

Variable	HIV infected (n = 1189)	HIV uninfected (n = 1179)	Total (n = 2368)	P
Enrollment clinic				
Rural	513 (43.1%)	642 (54.5%)	1155 (48.8%)	<0.001
Peri-urban	448 (37.7%)	355 (30.1%)	803 (33.9%)	
Urban	228 (19.2%)	182 (15.6%)	410 (17.3%)	
Place of delivery				
Home/other[a]	141 (11.8%)	139 (11.8%)	280 (11.8%)	0.959
Hospital/clinic	1048 (88.1%)	1040 (88.2%)	2088 (88.2%)	
Type of delivery				
Cesarean	166 (13.9%)	149 (12.6%)	315 (13.3%)	0.638
Vaginal	1022 (86.0%)	1029 (87.3%)	2051 (86.6%)	
Missing	1 (0.1%)	1 (0.1%)	2 (0.1%)	
Birthweight (g)				
≥2500	1072 (90.2%)	1098 (93.1%)	2170 (91.6%)	0.009
<2500	117 (9.8%)	81 (6.9%)	198 (8.4%)	
Gestational age				
≥37 weeks	930 (78.2%)	932 (79.1%)	1862 (78.6%)	0.963
34 to <37 weeks	183 (15.4%)	173 (14.7%)	356 (15.0%)	
32 to <34 weeks	47 (4.0%)	45 (3.8%)	92 (3.9%)	
<32 weeks	29 (2.4%)	29 (2.4%)	58 (2.5%)	
Size for gestation				
≥10%	974 (81.9%)	1001 (84.9%)	1975 (83.4%)	0.051
3 to <10%	121 (10.2%)	105 (8.9%)	226 (9.5%)	
<3%	94 (7.9%)	73 (6.2%)	167 (7.1%)	
Maternal variables (median, IQR)				
Age (years)	25.1 (21.6–29.6)	21.8 (19.1–27.7)	23.6 (20.1–28.8)	<0.001
Weight	61.8 (55.7–69.5)	62.6 (56.3–70.4)	62.2 (56.0–69.8)	0.017
Height	158.1 (154.2–162.6)	158.5 (154.9–163.0)	158.4 (154.5–162.8)	0.060
BMI	24.9 (22.4–27.6)	24.6 (22.6–27.8)	24.7 (22.5–27.7)	0.951
MUAC	27.1 (25.0–29.5)	27.1 (25.0–29.7)	27.1 (25.0–29.6)	0.243

P indicates the statistical difference between HIV infected and HIV uninfected.
[a]Other place of delivery refers to deliveries on the way to hospital or clinic.

infants were SGA. There were 393 (16.6%) infants were SGA; two-fifths of these were severely growth restricted and 36 (9.2%) of the SGA births were preterm. The percentage of SGA infants was higher for HIV-positive than for HIV-negative women (18.1 and 15.1% respectively, $P = 0.051$). Similarly, the proportion of preterm deliveries was slightly higher in HIV-positive than in HIV-negative women, although this was not statistically significant (21.8 and 20.9%, respectively, $P = 0.621$).

Stratifying by the child's HIV status: 26 (23.6%) of the perinatally infected, 9 (15.8%) of the post-natally infected and 318 (16.3%) of the uninfected children were SGA, $P = 0.378$, while 26 (23.6%), 13 (22.8%) and 417 (21.4%), respectively, were preterm, $P = 0.722$.

Risk factors for SGA and prematurity

Table II presents the overall risk factors for SGA and prematurity. The probability of an SGA infant significantly increased with maternal HIV-infection after adjusting for other factors, known to be associated with SGA risk. Additionally, compared with the relevant reference categories, infants residing in a household without piped water (a proxy indicator of lower socio-economic status) had a significantly higher probability of being SGA, as were first born, those born at home, and those whose mother's height at birth was below the study population mean.

Among HIV-positive mothers, those residing in a household without piped water (adjusted prevalence ratio (aRR): 1.34, 95% CI: 1.05–1.71), delivering at home (aRR: 1.59, 95% CI: 1.17–2.16), delivering for the first time (aRR: 1.59, 95% CI: 1.24–2.04) or of shorter stature (aRR: 1.81, 95% CI: 1.21–2.68) were at a significantly higher probability of having an SGA infant. Additionally, infants of HIV-positive mothers with CD4 counts below 200 cells/mm³ had a higher probability of being SGA (aRR: 1.43, 95% CI: 1.00–2.07, $P = 0.053$). In HIV-negative mothers, after adjusting for all other factors in Table II, parity was the only factor significantly associated with SGA, with first born infants having a higher probability of being SGA (aRR: 1.97, 95% CI: 1.42–2.73).

Table II Risk factors for SGA and preterm birth ($n = 2368$).

Variable	Overall live births [n (%)]	SGA unadjusted RR (95% CI)	P	SGA adjusted RR (95% CI)	P	Preterm unadjusted RR (95% CI)	P	Preterm adjusted RR (95% CI)	P
Infant gender									
Female	1188 (50.2)	1.00				1.00			
Male	1178 (49.8)	1.09 (0.91–1.31)	0.329			1.01 (0.86–1.18)	0.909		
Area									
Rural	1161 (49.0)	1.00				1.00			
Peri-urban	807 (34.1)	0.92 (0.75–1.13)	0.424			0.90 (0.63–1.28)	0.552		
Urban	400 (16.9)	1.00 (0.78–1.28)	0.994			0.91 (0.58–1.42)	0.675		
Water source									
Piped	1601 (67.6)	1.00		1.00		1.00			
Non-piped	706 (29.8)	1.29 (1.07–1.56)	0.008	1.26 (1.04–1.51)	0.017	1.85 (0.71–2.02)	0.077		
Missing data	61 (2.6)	0.73 (0.36–1.49)	0.392	0.71 (0.35–1.43)	0.337	1.31 (0.88–1.95)	0.186		
Toilet type									
Flush	398 (16.8)	1.00				1.00			
Non-flush	1378 (58.2)	0.99 (0.76–1.27)	0.910			1.13 (0.90–1.41)	0.284		
None	531 (22.4)	1.36 (1.02–1.79)	0.032			1.15 (0.89–1.49)	0.276		
Missing data	61 (2.6)	0.72 (0.35–1.50)	0.387			1.52 (0.98–2.36)	0.058		
Delivery place									
Hospital/ clinic	2088 (88.2)	1.00		1.00		1.00		1.00	
Home/ other	208 (11.8)	1.34 (1.05–1.72)	0.018	1.48 (1.16–1.90)	0.002	1.36 (1.11–1.67)	0.004	1.38 (1.12–1.69)	0.002
Parity									
1–3	1155 (48.8)	1.00		1.00		1.00			
0	1018 (43.0)	1.58 (1.30–1.91)	<0.001	1.71 (1.41–2.07)	<0.001	1.02 (0.87–1.19)	0.840		
≥4	195 (8.2)	1.26 (0.88–1.78)	0.203	1.24 (0.87–1.77)	0.241	0.76 (0.54–1.06)	0.106		
Maternal age									
>30 years	509 (21.5)	1.00				1.00		1.00	
20–30 years	1275 (53.8)	0.96 (0.76–1.22)	0.763			1.18 (0.95–1.45)	0.133	1.15 (0.92–1.43)	0.196
<20 years	582 (24.6)	1.10 (0.85–1.43)	0.458			1.31 (1.03–1.65)	0.025	1.30 (1.02–1.66)	0.033
Missing data	2 (0.1)								
Maternal HIV									
HIV negative	1179 (49.8)	1.00		1.00		1.00		1.00	
HIV positive	1189 (50.2)	1.20 (1.00–1.44)	0.052	1.28 (1.06–1.53)	0.009	1.39 (0.89–1.21)	0.621	1.07 (0.91–1.26)	0.380
Maternal education									
No education	139 (5.9)	1.00				1.00			
Some primary	811 (34.2)	1.05 (0.58–1.93)	0.858			1.74 (0.76–3.97)	0.189		
Secondary and tertiary	1418 (59.9)	1.08 (0.60–1.94)	0.794			1.72 (0.77–3.85)	0.186		
Maternal weight									
≥Mean	823 (33.5)	1.00				1.00		1.00	
<Mean	1039 (42.3)	1.44 (1.15–1.79)	0.002			1.35 (1.13–1.62)	0.001	1.28 (1.07–1.54)	0.008
Missing data	592 (24.1)	1.47 (1.15–1.89)	0.002			1.04 (0.83–1.29)	0.741	1.01 (0.81–1.27)	0.893
Maternal height									
≥Mean	661 (26.9)	1.00		1.00		1.00			
<Mean	672 (27.4)	1.33 (1.02–1.74)	0.032	1.36 (1.05–1.77)	0.020	1.11 (0.91–1.37)	0.297		
Missing data	1121 (45.7)	1.43 (1.12–1.82)	0.003	1.41 (1.11–1.79)	0.005	0.95 (0.78–1.15)	0.591		

Continued

Table II *Continued*

Variable	Overall live births [n (%)]	SGA unadjusted RR (95% CI)	P	SGA adjusted RR (95% CI)	P	Preterm unadjusted RR (95% CI)	P	Preterm adjusted RR (95% CI)	P
Maternal MUAC									
≥Mean	789 (32.2)	1.00				1.00			
<Mean	1039 (42.3)	1.33 (1.06–1.67)	0.013			1.38 (1.15–1.66)	0.001		
Missing data	626 (25.5)	1.39 (1.09–1.78)	0.009			1.10 (0.88–1.37)	0.418		

RR, relative risk.

Additional analyses were carried out to assess the effect of maternal HIV infection on the risk of delivering severely growth-restricted infants (<3% birthweight-for-gestational age percentile). Adjusting for the risk factors in the final model, infants born to HIV-positive mothers had higher probability of severe growth restriction than those of HIV-negative mothers, although this did just not reach statistical significance due to lack of statistical power (aRR: 1.33, 95% CI: 0.98–1.79; P = 0.067).

In both univariate and multivariable analyses, the probability of preterm delivery was not significantly associated with maternal HIV infection (Table II). However, probability of preterm delivery was significantly higher in infants born at home, as well as in those born to mothers aged less than 20 years and mothers whose maternal weight at birth was less than the population mean. Among HIV-positive women, delivery place was the only statistically significant variable, with children born at home having significantly higher probability of being preterm (aRR: 1.46, 95% CI: 1.11–1.93). Among HIV-negative women, maternal weight at birth was the only significant variable, with children born to mothers whose weight was below the population mean having a significantly higher probability of being preterm (aRR: 1.31, 95% CI: 1.01–1.71).

Additional analyses showed that maternal HIV infection was not associated with severe prematurity (<34 weeks), after adjusting for other risk factors (aRR: 1.08, 95% CI: 0.78–1.50; P = 0.628).

Mortality

Overall, 5.8% (137/2368) infants died in the first year of life: 9.3% (111/1189) of infants of HIV-positive mothers and 2.2% (26/1179) of infants of HIV-negative mothers (P < 0.001). Infants born to HIV-positive women were at significantly higher risk of mortality compared with those of HIV-negative women (IMR, 93.4 and 22.1 per 1000 live births, P < 0.001). Additionally, HIV infected infants were also at a significantly higher mortality risk that uninfected infants (IMR 370.7 and 27.2 per 1000 live births, P < 0.001). Crude neonatal and infant mortality rates did not differ significantly between term and preterm births: 6.4 and 3.9 per 1000 live births, P = 0.522 for neonates and 56.4 and 63.2 per 1000 live births, P = 0.561 for infants respectively.

However, both crude neonatal and infant mortality rates differed significantly between AGA and SGA infants. SGA neonates had a mortality rate of 20.4 per 1000 live births, 6-fold higher than those AGA at 3.0 per 1000 live births, P < 0.001. Infant mortality rates among SGA infants was 101.8 per 1000 live births, double the rate among AGA infants at 49.1 per 1000 live births, P < 0.001. We estimated that at
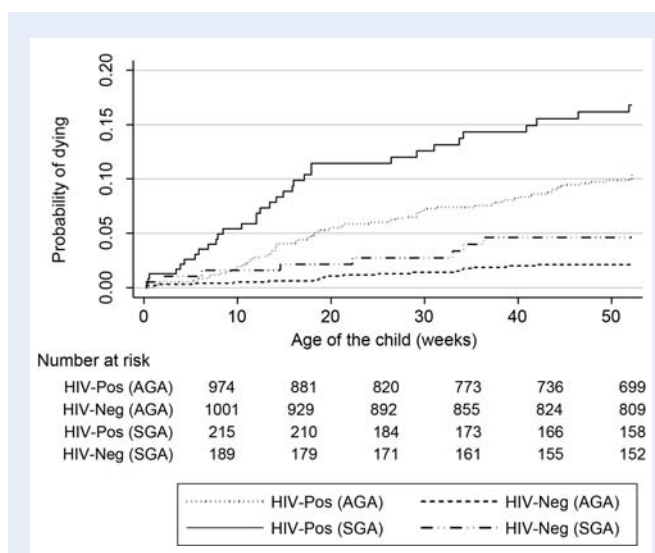
Figure 2 Estimated infant mortality by 12 months of age by maternal HIV status and size for gestational age.

age 12 months, 16% of SGA and 10% of AGA infants (P = 0.008) of HIV-positive mothers will have died and 5% of SGA and 2.5% of AGA infants (P = 0.079) of negative mothers will have died (Fig. 2).

Factors associated with infant mortality

Table III shows the risk factors for all children in the cohort irrespective of maternal HIV status. The CD4 count variable includes 1179 HIV-negative mothers classified as 'missing'. The 2368 infants were followed up for a total of 25 305 child-months over their first year of life. Overall, compared with those AGA, SGA infants had a 2-fold significantly increased hazard of death; and severely growth-restricted infants (<3% percentile) had higher hazards of mortality than those with less severe growth restriction (Table III). Overall, preterm infants had a slightly increased risk of death; this did not reach statistical significance in either univariate or multivariate analyses. Lower maternal age was associated with a significantly increased hazard and women with some formal education had a reduced hazard of infant death.

Infants of HIV-positive mothers had a 3-fold significantly increased hazard of death; those whose mothers had antenatal CD4 counts <200 cells/mm^3 had a 2-fold significantly increased hazard of death compared with those whose mothers had CD4 counts of at

Table III Risk factors for infant mortality (*n* = 2368).

Variable	Overall live births [*n* (%)]	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Gestational age					
≥37 weeks	1862 (78.6)	1.00		1.00	
34–36 weeks	356 (15.1)	1.10 (0.69–1.74)	0.688	1.18 (0.79–1.79)	0.423
<34 weeks	150 (6.3)	1.17 (0.54–2.55)	0.685	1.31 (0.58–2.94)	0.509
Size for gestation					
≥10% (AGA)	1975 (83.4)	1.00		1.00	
3 to <10% (SGA)	226 (9.5)	2.27 (1.29–4.02)	0.004	2.12 (1.18–3.81)	0.012
<3% (SGA)	167 (7.1)	3.91 (2.31–6.63)	<0.001	2.77 (1.56–4.91)	<0.001
Area					
Rural	1161 (49.0)	1.00		1.00	
Peri-urban	807 (34.1)	0.86 (0.55–1.33)	0.496	0.73 (0.47–1.14)	0.172
Urban	400 (16.9)	0.28 (0.11–0.69)	0.006	0.25 (0.10–0.67)	0.004
Parity					
1–3	1155 (48.8)	1.00		1.00	
0	1018 (43.0)	1.09 (0.72–1.67)	0.666	0.94 (0.57–1.57)	0.824
≥4	195 (8.2)	0.49 (0.17–1.36)	0.170	0.71 (0.23–2.22)	0.559
Maternal age					
>30 years	509 (21.5)	1.00		1.00	
20–30 years	1275 (53.8)	1.62 (0.90–2.92)	0.108	1.59 (0.81–3.12)	0.179
<20 years	582 (24.6)	1.59 (0.83–3.06)	0.165	2.34 (1.01–5.43)	0.047
Missing data	2 (0.1)				
Maternal education					
No education	139 (5.9)	1.00		1.00	
Some primary	811 (34.2)	0.53 (0.25–1.12)	0.097	0.28 (0.13–0.61)	0.002
Secondary and tertiary	1418 (59.9)	0.60 (0.30–1.21)	0.155	0.37 (0.17–0.80)	0.011
Child HIV infection status					
Uninfected	1945 (82.1)	1.00		1.00	
Perinatally infected	109 (4.6)	24.39 (15.10–39.39)	<0.001	18.43 (10.40–32.65)	<0.001
Post-natally infected	57 (2.4)	5.42 (2.56–11.48)	<0.001	5.06 (2.32–11.01)	<0.001
Infected, timing unknown	40 (1.7)	12.04 (4.32–33.53)	<0.001	7.43 (2.56–21.60)	<0.001
Missing data	217 (9.2)	5.15 (2.42–10.91)	<0.001	5.02 (2.35–10.73)	<0.001
Maternal HIV status					
HIV negative	1179 (49.8)	1.00			
HIV positive	1189 (50.2)	3.02 (1.91–4.79)	<0.001		
Maternal antenatal CD4 count					
≥500 cells/mm^3	498 (21.0)	1.00		1.00	
200–499 cells/mm^3	524 (22.1)	1.86 (1.06–3.25)	0.030	1.37 (0.77–2.46)	0.285
<200 cells/mm^3	129 (5.5)	2.47 (1.15–5.31)	0.021	1.87 (1.21–3.96)	0.009
Missing data[a]	1217 (51.4)	0.54 (0.29–0.96)	0.037	0.73 (0.41–1.27)	0.267

HR, hazard ratio. aHR were adjusted for the other variables in the table. Maternal HIV status was not adjusted for in the multivariable analysis as only HIV-positive women had an antenatal CD4 count. *Note*: toilet type, water source, child gender and delivery place were not significantly associated with infant mortality.
[a]Missing CD4 count category includes 1179 HIV-negative women.

least 500 cells/mm^3, when categorizing HIV-negative mothers as 'missing'.

Overall, 8.7% (206/2368) of infants were HIV infected in the first year of life. Of the 109 perinatally infected infants, 24 (22.0%) were SGA and 27 (24.8%) were preterm (*P* = 0.562). The 206 HIV-infected infants were at a significantly increased risk of mortality compared with those who were HIV uninfected, allowing for child HIV status as a time-varying variable (Table III).

Discussion

This cohort study enrolled HIV-infected and -uninfected pregnant women between 2001 and 2004 (before the availability of antiretroviral treatment), in rural South Africa; almost all pregnant women in this setting present for antenatal visits (Hoque et al., 2008), and the study enrollment rate was >80% (Bland et al., 2010). In a recent systematic review, Northern and Western Africa had, respectively, an estimated rate of preterm births of 8.7 and 10.1%, considerably lower compared with that in Southern Africa, at 17.5% (Beck et al., 2010). Preterm births have multiple causes, and the design of this study allowed us to investigate the contribution of HIV, if any, given the enrolment of both HIV-infected and -uninfected women, in a setting with a very high antenatal HIV prevalence estimated at 39.5% (Department of Health, 2010a,b) and high preterm delivery rates. The prevalence of preterm deliveries was 21.4% while that of SGA was 16.6%, with limited overlap between the two, and the maternal HIV infection was associated with a 1.2-fold increased risk of SGA birth. This significant association was maintained after controlling for water source, delivery place, parity and maternal height, factors associated with SGA in other studies (Verhoeff et al., 2001; Bhutta et al., 2005).

SGA infants were at a significantly increased hazard of infant mortality compared with those who were AGA, but there was no difference in mortality between the term and preterm births. Our findings of increased infant mortality among SGA infants are consistent with another African study (Kasirye-Bainda and Musoke, 1992), with the risk increasing with severity of growth restriction, such that severely SGA infants had a 3-fold significantly increased hazard of death before and after adjusting for other confounders. A plausible mechanism for this may be the increased post-natal morbidity rates (Kasirye-Bainda and Musoke, 1992). As infant follow-up stopped at 2 years, we were not able to explore longer term implications of preterm delivery, such as developmental disabilities and cerebral palsy. Generally, there is limited service provision for children with such problems in this setting.

Knowledge of the independent effect of maternal HIV infection on birth outcomes such as preterm delivery and SGA infants is needed in order to understand the potential impact of antiretroviral treatment. Additionally, quantifying the burden of neonatal and infant morbidity and mortality associated with maternal HIV is important in similar settings with high antenatal HIV prevalence. Our study, conducted before antiretroviral treatment was available in this setting, shows that maternal HIV infection was not significantly associated with preterm delivery, consistent with other studies in Africa (Bulterys et al., 1994; Verhoeff et al., 2001). However, this contrast to earlier African studies which enrolled hospital-based deliveries only (Habib et al., 2008; Laar et al., 2010), while our study enrolled deliveries from both in and outside hospitals. Further, in one of the studies, 31% of pregnant women were lost prior to delivery, a large proportion of these were HIV negative, which may affect the strength of the association reported (Laar et al., 2010). Infants delivered at home had higher probabilities of being preterm, probably due to the fact that these women were unable to reach a healthcare facility in time. Other independent factors associated with preterm delivery in this and previous studies were younger maternal age, consistent with greater perinatal risks due to social disadvantages or biological factors (da Silva et al., 2003) and low maternal weight (Ehrenberg et al., 2003).

The current prevention of mother-to-child transmission (PMTCT) guidelines in South Africa recommend zidovudine (AZT) from 14 weeks of pregnancy, single-dose nevirapine, 3-hourly AZT intrapartum and a single dose of tenofovir and emtracitabine post-partum, for women not eligible for lifelong antiretroviral treatment and antiretroviral treatment for those eligible starting as soon as possible in pregnancy (Department of Health, 2010a, b). Several studies in Europe and the USA have reported an increased risk of preterm delivery with antenatal highly active antiretroviral therapy (HAART), with associations of between 1.5- and 3.5-fold increased risk (Thorne et al., 2004; Cotter et al., 2006; Townsend et al., 2010a,b) and there are also preliminary indications from studies in sub-Saharan Africa (SSA) of the same association (Powis et al., 2011; van der Merwe et al., 2011). This has been hypothesized to be due to an immunological mechanism, with HAART in pregnancy associated with a reversal of the Th1 to Th2 switch that is an immunological feature of normal pregnancy (Fiore et al., 2006) rather than being caused by infant or placental factors. Given the enormous benefits of HAART for maternal health and PMTCT, and the fact that most of these preterm infants are born from gestations associated with relatively low morbidity and mortality risk, the benefits are considered to outweigh the risks in resource-rich settings (de Ruiter et al., 2008). In a UK study, the incremental risk−benefit ratio of HAART compared with monotherapy with respect to preterm delivery was modelled and it was found that each 10 infant infections prevented through the use of antenatal HAART would result in an additional 6 preterm births (Townsend et al., 2010a,b).

Despite the resource-limited setting, preterm infants in our study (37% of whom were born at 36 weeks) had good survival and we observed no difference in the crude neonatal and infant mortality rates comparing term and preterm deliveries. In the multivariable analysis, there was no statistically significant difference in infant mortality between the two groups, allowing for time-varying child infection status, although the hazard of death was slightly higher for preterm infants. The VTS was not designed to investigate the role of preterm delivery in infant mortality; furthermore, the implementation of 'Kangaroo mother care (KMC; continous skin-to-skin contact and support for exclusive breastfeeding or other appropriate feeding) in the first week of life within the study, shown to significantly reduce neonatal mortality and serious morbidity amongst preterm infants in low- and middle-income countries (Lawn et al., 2010), may have resulted in better outcomes than would be seen in other similar settings where KMC remains unavailable (Department of Health, 2008).

In the context of ongoing scale-up of antiretroviral treatment in SSA (Mutevedzi et al., 2010), a growing number of pregnant women with HIV will be using combination antiretroviral treatment throughout pregnancy (Townsend et al., 2008). The benefits of antenatal combination antiretroviral treatment in PMTCT in an African setting were illustrated in the Mma Bana trial in Botswana, with MTCT rates of 1.1% (Shapiro et al., 2010). Maternal initiation of HAART also has benefits of increased survival chances for the woman herself (Herbst et al., 2009) and indirectly that of her children (Ndirangu et al., 2010). Preliminary indications of the same association between HAART use and increased risk of preterm delivery in African populations as reported in resource-rich settings (Powis et al., 2011; van der Merwe et al., 2011)

highlight the need for evaluation of the potential risks as well as the benefits of antenatal HAART.

Our finding of an increased risk of SGA in infants of HIV-positive mothers accords with previous studies elsewhere in Africa (Bulterys *et al.*, 1994; Taha *et al.*, 1995), as does our identification of primiparae and shorter maternal height as important contributors to SGA (Kramer, 1987a,b; Verhoeff *et al.*, 2001; Watson-Jones *et al.*, 2007), together with lower socio-economic status, included here with the use of a proxy measure (lack of piped water). Co-infections, for instance malaria and other medical conditions like tuberculosis and anaemia prior to or early in pregnancy have been shown to be important factors associated with SGA and preterm delivery (Verhoeff *et al.*, 2001; Noble *et al.*, 2005; Watson-Jones *et al.*, 2007). In this study, such data were not available, although malaria is not an issue in KwaZulu-Natal. We were also unable to adjust for factors such as smoking, hypertension and anaemia.

In common with other studies reporting associations between advanced maternal HIV disease and adverse birth outcomes (Kuhn *et al.*, 2005; Mehta *et al.*, 2008), we found that HIV-positive women with severe immunodeficiency had higher risk of having a SGA infant. This raises the possibility that improving maternal health with the use of antiretroviral treatment might result in better fetal growth and fewer SGA infants. Although HAART regimens have been implicated in preterm delivery, this does not appear to be the case for IUGR according to a French study (Briand *et al.*, 2009). However, recent evidence from Botswana suggesting that maternal antiretroviral treatment initiation before conception may be associated with very SGA infants (Parekh *et al.*, 2011) needs confirmation, particularly given the potential for confounding by indication due to the limited ability to adjust for maternal disease status in this study.

In the current study of HIV-positive and -negative women, one in five deliveries occurred preterm, but this was not associated with maternal HIV status, nor was it a risk factor for infant mortality. However, one in six deliveries were of SGA infants and maternal HIV was one of the factors associated with this outcome. Furthermore, SGA infants, particularly those with HIV-positive mothers, were at increased risk of death in the first year of life. This has implications for clinical practice. Whereas preterm infants are usually routinely followed-up for several months post-delivery, SGA infants are not. Our findings suggest that SGA infants should also be included in careful clinical follow-up to minimize morbidity and mortality. Ongoing research and monitoring in SSA is needed to provide more information on the complex relationships between maternal health, antenatal ART and pregnancy outcomes in this setting where ~90% of the world's HIV-infected pregnant women live. Future studies of preterm birth and SGA should include variables such as hypertension, anaemia and tuberculosis co-infections, although the feasibility of carrying out such a study on a large rural African population is questionable.

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Authors' roles

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Conflict of interest

None declared.

References

Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan MA. United States national reference for fetal growth. *Obstet Gynecol* 1996;**87**:163–168.

Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, Menon R, Van Look PF. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ* 2010;**88**:31–38.

Bhutta ZA, Darmstadt GL, Hasan BS, Haws RA. Community-based interventions for improving perinatal and neonatal health outcomes in developing countries: a review of the evidence. *Pediatrics* 2005; **115**:519–617.

Bland RM, Rollins NC, Coovadia HM, Coutsoudis A, Newell ML. Infant feeding counselling for HIV-infected and uninfected women: appropriateness of choice and practice. *Bull World Health Organ* 2007; **85**:289–296.

Bland R, Coovadia H, Coutsoudis A, Rollins N, Newell M. Cohort profile: mamanengane or the Africa centre vertical transmission study. *Int J Epidemiol* 2010;**39**:351–360.

Briand N, Mandelbrot L, Le Chenadec J, Tubiana R, Teglas JP, Faye A, Dollfus C, Rouzioux C, Blanche S, Warszawski J. No relation between in-utero exposure to HAART and intrauterine growth retardation. *AIDS* 2009;**23**:1235–1243.

Brocklehurst P, French R. The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis. *Br J Obstet Gynaecol* 1998;**105**:836–848.

Bruin J. Newtest: command to compute new test. UCLA: Academic Technology Services, Statistical Consulting Group, 2006. http://www.ats.ucla.edu/stat/stata/ado/analysis/ (14 July 2011, date last accessed).

Bulterys M, Chao A, Munyemana S, Kurawige JB, Nawrocki P, Habimana P, Kageruka M, Mukantabana S, Mbarutso E, Dushimimana A et al. Maternal human immunodeficiency virus 1 infection and intrauterine growth: a prospective cohort study in Butare, Rwanda. *Pediatr Infect Dis J* 1994;**13**:94–100.

Coovadia HM, Rollins NC, Bland RM, Little K, Coutsoudis A, Bennish ML, Newell ML. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet* 2007;**369**:1107–1116.

Costello A, Francis V, Byrne A, Puddephatt C. *Saving Newborn Lives: State of the World's Newborns*. Washington, DC 20036: Save the Children, 2001.

Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis* 2006;**193**:1195–1201.

Coutinho LMS, Scazufca M, Menezes PR. Methods for estimating prevalence rates in cross-sectional studies. *Rev Saude Publica* 2008; **42**:992–998.

da Silva AA, Simoes VM, Barbieri MA, Bettiol H, Lamy-Filho F, Coimbra LC, Alves MT. Young maternal age and preterm birth. *Paediatr Perinat Epidemiol* 2003;**17**:332–339.

de Onis M, Onyango AW, Van den Broeck J, Chumlea WC, Martorell R. Measurement and standardization protocols for anthropometry used in the construction of a new international growth reference. *Food Nutr Bull* 2004;**25**:S27–S36.

de Ruiter A, Mercey D, Anderson J, Chakraborty R, Clayden P, Foster G, Gilling-Smith C, Hawkins D, Low-Beer N, Lyall H et al. British HIV association and children's HIV association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med* 2008;**9**:452–502.

Department of Health. Strategic plan for maternal, neonatal, child and women's health (MNCWH) and nutrition in South Africa, 2009–2014, 2008. www.ecdoh.gov.za/uploads/files/160709191744.doc (8 February 2012, last date accessed).

Department of Health. National antenatal sentinel HIV and syphilis prevalence survey in South Africa, 2009. Pretoria: Department of Health, 2010a.

Department of Health. Clinical guidelines: PMTCT (prevention of mother-to-child transmission). Pretoria: South African Naional AIDS Council, 2010b.

Ehrenberg HM, Dierker L, Milluzzi C, Mercer BM. Low maternal weight, failure to thrive in pregnancy, and adverse pregnancy outcomes. *Am J Obstet Gynecol* 2003;**189**:1726–1730.

Euser AM, de Wit CC, Finken MJ, Rijken M, Wit JM. Growth of preterm born children. *Horm Res* 2008;**70**:319–328.

Fiore S, Newell ML, Trabattoni D, Thorne C, Gray L, Savasi V, Tibaldi C, Ferrazzi E, Clerici M. Antiretroviral therapy-associated modulation of Th1 and Th2 immune responses in HIV-infected pregnant women. *J Reprod Immunol* 2006;**70**:143–150.

Habib NA, Daltveit AK, Bergsjo P, Shao J, Oneko O, Lie RT. Maternal HIV status and pregnancy outcomes in northeastern Tanzania: a registry-based study. *BJOG* 2008;**115**:616–624.

Herbst AJ, Cooke GS, Barnighausen T, KanyKany A, Tanser F, Newell ML. Adult mortality and antiretroviral treatment roll-out in rural KwaZulu-Natal, South Africa. *Bull World Health Organ* 2009; **87**:754–762.

Hoque M, Hoque E, Kader SB. Audit of antenatal care in a rural district of KZN, South Africa. *South Afr Family Practice* 2008;**50**:66.

Kasirye-Bainda E, Musoke FN. Neonatal morbidity and mortality at Kenyatta National Hospital newborn unit. *East Afr Med J* 1992; **69**:360–365.

Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. *Bull World Health Organ* 1987a;**65**:663–737.

Kramer MS. Intrauterine growth and gestational duration determinants. *Pediatrics* 1987b;**80**:502–511.

Kuhn L, Kasonde P, Sinkala M, Kankasa C, Semrau K, Scott N, Tsai WY, Vermund SH, Aldrovandi GM, Thea DM. Does severity of HIV disease in HIV-infected mothers affect mortality and morbidity among their uninfected infants? *Clin Infect Dis* 2005;**41**:1654–1661.

Laar AK, Ampofo W, Tuakli JM, Norgbe GK, Quakyi IA. Preterm delivery and low birth weight among neonates born to HIV-positive and HIV-negative Ghanaian women. *J Public Health Epidemiol* 2010; **2**:224–237.

Langston C, Lewis DE, Hammill HA, Popek EJ, Kozinetz CA, Kline MW, Hanson IC, Shearer WT. Excess intrauterine fetal demise associated with maternal human immunodeficiency virus infection. *J Infect Dis* 1995;**172**:1451–1460.

Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? where? why? *Lancet* 2005;**365**:891–900.

Lawn JE, Mwansa-Kambafwile J, Horta BL, Barros FC, Cousens S. 'Kangaroo mother care' to prevent neonatal deaths due to preterm birth complications. *Int J Epidemiol* 2010;**39**(Suppl. 1):i144–i154.

Lin DY, Wei LJ. The robust inference for the Cox Proportional Hazards Model. *J Am Stat Assoc* 1989;**84**:1074–1078.

Mansour E, Eissa AN, Nofal LM, Kharboush I, Sallam I. Incidence and factors leading to low birth weight in Egypt. *Int Pediatr* 2002; **17**:223–230.

Mehta S, Manji KP, Young AM, Brown ER, Chasela C, Taha TE, Read JS, Goldenberg RL, Fawzi WW. Nutritional indicators of adverse pregnancy outcomes and mother-to-child transmission of HIV among HIV-infected women. *Am J Clin Nutr* 2008;**87**:1639–1649.

Mutevedzi PC, Lessells RJ, Heller T, Barnighausen T, Cooke GS, Newell ML. Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes? *Bull World Health Organ* 2010;**88**:593–600.

Ndirangu J, Newell ML, Tanser F, Herbst AJ, Bland R. Decline in early life mortality in a high HIV prevalence rural area of South Africa: evidence of HIV prevention or treatment impact? *AIDS* 2010;**24**:593–602.

Noble A, Ning Y, Woelk GB, Mahomed K, Williams MA. Preterm delivery risk in relation to maternal HIV infection, history of malaria and other infections among urban Zimbabwean women. *Cent Afr J Med* 2005; **51**:53–58.

Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr* 2003;**3**:6.

Parekh N, Ribaudo H, Souda S, Chen J, Mmalane M, Powis K, Essex M, Makhema J, Shapiro RL. Risk factors for very preterm delivery and delivery of very-small-for-gestational-age infants among HIV-exposed and HIV-unexposed infants in Botswana. *Int J Gynaecol Obstet* 2011; **115**:20–25.

Powis KM, Kitch D, Ogwu A, Hughes MD, Lockman S, Leidner J, van Widenfelt E, Moffat C, Moyo S, Makhema J et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. *J Infect Dis* 2011;**204**:506–514.

Rayco-Solon P, Fulford AJ, Prentice AM. Differential effects of seasonality on preterm birth and intrauterine growth restriction in rural Africans. *Am J Clin Nutr* 2005;**81**:134–139.

Rollins NC, Coovadia HM, Bland RM, Coutsoudis A, Bennish ML, Patel D, Newell ML. Pregnancy outcomes in HIV-infected and uninfected women in rural and urban South Africa. *J Acquir Immune Defic Syndr* 2007; **44**:321–328.

Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, Makhema J, Moyo S, Thior I, McIntosh K et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med* 2010; **362**:2282–2294.

Taha TE, Dallabetta GA, Canner JK, Chiphangwi JD, Liomba G, Hoover DR, Miotti PG. The effect of human immunodeficiency virus infection on birthweight, and infant and child mortality in urban Malawi. *Int J Epidemiol* 1995;**24**:1022–1029.

Tanser F. Methodology for optimising location of new primary health care facilities in rural communities: a case study in KwaZulu-Natal, South Africa. *J Epidemiol Community Health* 2006;**60**:846–850.

Temmerman M, Plummer FA, Mirza NB, Ndinya-Achola JO, Wamola IA, Nagelkerke N, Brunham RC, Piot P. Infection with HIV as a risk factor for adverse obstetrical outcome. *AIDS* 1990;**4**:1087–1093.

Temmerman M, Chomba EN, Ndinya-Achola J, Plummer FA, Coppens M, Piot P. Maternal human immunodeficiency virus-1 infection and pregnancy outcome. *Obstet Gynecol* 1994;**83**:495–501.

Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. *AIDS* 2004;**18**:2337–2339.

Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Trends in management and outcome of pregnancies in HIV-infected women in the UK and Ireland, 1990–2006. *BJOG* 2008;**115**:1078–1086.

Townsend CL, Tookey PA, Newell ML, Cortina-Borja M. Antiretroviral therapy in pregnancy: balancing the risk of preterm delivery with prevention of mother-to-child HIV transmission. *Antivir Ther* 2010a; **15**:775–783.

Townsend C, Schulte J, Thorne C, Dominguez KI, Tookey PA, Cortina-Borja M, Peckham CS, Bohannon B, Newell ML. Antiretroviral therapy and preterm delivery—a pooled analysis of data from the United States and Europe. *BJOG* 2010b;**117**:1399–1410.

van der Merwe K, Hoffman R, Black V, Chersich M, Coovadia A, Rees H. Birth outcomes in South African women receiving highly active antiretroviral therapy: a retrospective observational study. *J Int AIDS Soc* 2011;**14**:42.

Verhoeff FH, Brabin BJ, van Buuren S, Chimsuku L, Kazembe P, Wit JM, Broadhead RL. An analysis of intra-uterine growth retardation in rural Malawi. *Eur J Clin Nutr* 2001;**55**:682–689.

Villar J, Belizan JM. The relative contribution of prematurity and fetal growth retardation to low birth weight in developing and developed societies. *Am J Obstet Gynecol* 1982;**143**:793–798.

Watson-Jones D, Weiss HA, Changalucha JM, Todd J, Gumodoka B, Bulmer J, Balira R, Ross D, Mugeye K, Hayes R *et al.* Adverse birth outcomes in United Republic of Tanzania—impact and prevention of maternal risk factors. *Bull World Health Organ* 2007;**85**:9–18.

WHO Working Group on Infant Growth. An evaluation of infant growth: the use and interpretation of anthropometry in infants. *Bull World Health Organ* 1995;**73**:165–174.

Zeitlin JA, Ancel PY, Saurel-Cubizolles MJ, Papiernik E. Are risk factors the same for small for gestational age versus other preterm births? *Am J Obstet Gynecol* 2001;**185**:208–215.