Pregnancy outcomes in HIV-positive women in Ukraine, 2000–12 (European Collaborative Study in EuroCoord): an observational cohort study

Emmanouil Bagkeris, Ruslan Malyuta, Alla Volokha, Mario Cortina-Borja, Heather Bailey, Claire L Townsend, Claire Thorne, for the Ukraine European Collaborative Study in EuroCoord

Summary

Background Women living with HIV are potentially at increased risk of adverse pregnancy outcomes, due to a range of factors, including immunosuppression, use of combination antiretroviral therapy (ART), and injecting drug use. Rates of mother-to-child transmission of HIV in Ukraine have declined to around 2–4%, but little is known about other pregnancy outcomes in this setting. We used data from an observational prospective cohort study to assess pregnancy outcomes among HIV-positive women in Ukraine.

Methods The European Collaborative Study (ECS) in EuroCoord is a continuing cohort study, established in Ukraine in 2000. Eligible women are those with a diagnosis of HIV infection before or during pregnancy (including intrapartum) who deliver liveborn babies at seven sites. Maternal sociodemographic, HIV-related, and delivery (mother and infant) data were collected with study-specific questionnaires. We used Poisson regression models to identify factors associated with preterm delivery (before 37 weeks' gestation) and small weight for gestational age (less than the tenth percentile of weight for gestational age), based on complete cases.

Findings Between January, 2000, and July, 2012, data were collected on 8884 HIV-positive mother and liveborn infant pairs. Median maternal age was 26·5 years (IQR 23·1–30·3). 832 (11%) women had WHO stage 3 or 4 HIV and 1474 (17%) had a history of injecting drug use. 7348 (83%) had received antenatal ART. Among 7435 for whom ART type was available, 4396 (50%) had received zidovudine monotherapy and 2949 (33%) combination ART. Preterm delivery was seen in 780 (9%, 95% CI 8–9) of 8860 births overall and in 77 (9%, 7–11) of 889 babies with small size for gestational age. Factors associated with preterm delivery were history of injecting drug use (adjusted risk ratio 1·64, 95% CI 1·38–1·95), no ART (2·94, 2·43–3·57 *vs* zidovudine monotherapy), antenatal combination ART (1·40, 1·14–1·73 *vs* zidovudine monotherapy), WHO stage 4 HIV (2·42, 1·71–3·41 *vs* WHO stage 1), and being in the most socially deprived group (1·38, 1·11–1·71). Small size for gestational age was associated with history of injecting drug use (adjusted RR 1·39, 95% CI 1·16–1·65), most socially deprived (1·32, 1·09–1·61), no ART (1·60, 1·32–1·94 *vs* zidovudine monotherapy), and antenatal combination ART (1·33, 1·12–1·60 *vs* zidovudine monotherapy).

Interpretation Some risk factors for adverse pregnancy outcomes were directly associated with HIV and treatment and others were shared with the general antenatal population. Monitoring of pregnancy outcomes in Ukraine will be important as use of antenatal combination ART increases.

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See Comment page e356

Population, Policy and Practice Programme, UCL Institute of Child Health, London, UK (E Bagkeris MSc, M Cortina-Borja PhD, H Bailey PhD, C L Townsend PhD, C Thorne PhD); **Perinatal Prevention of AIDS Initiative, Odessa, Ukraine** (R Malyuta MD); **and Shupyk National Medical Academy of Postgraduate Education, Kiev, Ukraine** (A Volokha MD)

Correspondence to: Dr Claire Thorne, Population, Policy and Practice Programme, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK **claire.thorne@ucl.ac.uk**

Introduction

The HIV epidemic in eastern Europe and central Asia continues to grow, with 88% of the region's new infections occurring in the Russian Federation and Ukraine.[1] Although injecting drug use has driven the HIV epidemic in these areas, heterosexual acquisition became the main transmission route in newly diagnosed individuals in Ukraine in 2008, and of 21631 new HIV cases diagnosed in 2013, 45% were in women.[2] Ukraine is a lower-middle-income country and treatment scale-up has been slow:[3] around 50000 people were receiving antiretroviral therapy (ART) by 2013,[4] which is roughly half of the estimated total who have indications for treatment according to WHO's 2010 guidelines.[1]

In the general population in Ukraine, maternal mortality is 23 per 100000 livebirths, and the infant mortality rate is nine per 1000 livebirths; 75% of pregnant women have at least six antenatal care visits.[5,6] Programmes for the prevention of mother-to-child transmission of HIV started in 2001, and included universal antenatal HIV testing and repeat testing in the third trimester, short-course zidovudine, single-dose nevirapine, or both, and provision of free infant formula.[7,8] Subsequently, zidovudine monotherapy was recommended for use from at least 28 weeks' gestation, and by 2007 the mother-to-child transmission rate had fallen to around 7%.[7] In that year Ukraine adopted the WHO option B strategy of triple combination ART for all pregnant women, irrespective of clinical or immunological status.[9] Current rates of mother-to-child transmission are 2–4%.[2,9] National guidelines recommend elective caesarean delivery for HIV-positive women with a viral

Research in context

Evidence before this study

No studies of adverse birth outcomes among HIV-positive pregnant women in Ukraine have been reported. Published data on preterm delivery in eastern Europe are scarce, but individual studies have reported rates of 5–12% in the general population and 25% in HIV-positive women in Russia. Concerns about preterm delivery among HIV-positive women were first raised more than 20 years ago and focused initially on the effects of HIV and immunosuppression additional to traditional risk factors. Later the focus shifted to the effects of combination antiretroviral therapy (ART) regimens. Pregnancy outcomes in HIV-positive women need to be understood in the context of substantial variation between populations to inform country-specific programmes for prevention of mother-to-child transmission and maternal and child health.

Added value of this study

We assessed data on nearly 9000 HIV-positive women in Ukraine who delivered liveborn infants from 2000 to 2012. 9% of deliveries were preterm, and the cumulative prevalence of preterm delivery and small weight for gestational age was 18%. Our results indicate that in Ukraine overall at the end of this time period, around 720 babies born to HIV-positive women annually were preterm, small weight for gestational age, or both. Some risk factors are directly related to HIV infection, such as poor clinical status and use of combination ART, and others are shared with the general antenatal population, such as substance use and social deprivation. The increase in preterm delivery we saw over the 13 years of this study, independent of the scaling up of combination ART use since 2007, highlights the importance of monitoring outcomes and delineating contemporary risk factors, as antenatal combination ART coverage increases in this lower-middle-income setting.

Implications of all the available evidence

Our findings support previous evidence of an association between symptomatic HIV disease, AIDS, or severe immunodeficiency and risk of preterm delivery and are consistent with previous reports of an association between increased risk of adverse pregnancy outcomes and maternal substance use and social deprivation. The association we found between preterm delivery and combination ART in this study, which spanned a time period of changing use in Ukraine, requires further investigation. This study addresses an important evidence gap on the evolution of and risk factors for adverse pregnancy outcomes in this population. Our findings indicate the importance of ensuring that continuing efforts to improve perinatal outcomes in general are extended to HIV-positive women. We plan further research to assess the effects of antenatal combination ART as data accumulate on its use in Ukraine.

load greater than 1000 copies per mL, but access to monitoring of viral load has been limited[3] and methods of delivery vary substantially between clinical centres.[7]

Adverse birth outcomes, such as low birthweight, preterm delivery, and small size for gestational age, have multiple causes that are not well understood.[10] Associated risk factors include short maternal height, low or high body-mass index, uterine or placental abnormalities, illicit drug use, low socioeconomic status, smoking, unintended pregnancy, psychosocial stress, previous preterm delivery, infections, and multiple pregnancy.[10,11] Some, but not all, studies have identified maternal HIV infection as a risk factor for preterm delivery, low birthweight, and poor fetal growth, with women who have symptomatic disease or severe immunodeficiency being at the greatest risk.[12–14] Antenatal combination ART has been associated with increased risk of preterm delivery in HIV-positive women in studies in Europe, the USA, and Africa,[14–17] whereas other studies have found no association.

Pregnancy outcomes other than vertical HIV transmission have not yet been reported in HIV-positive women in Ukraine, but characterisation of these outcomes over the course of the epidemic so far is important to identify health priorities and to guide future work to explore the effects of specific interventions to prevent mother-to-child transmission. In this study we investigated birth outcomes and risk factors for adverse birth outcomes in HIV-positive women delivering over a 13 year period.

For **European Collaborative Study (ECS) in EuroCoord** see to http://www.EuroCoord.net

Methods

Study population

The population for this analysis was that enrolled in the European Collaborative Study (ECS) in EuroCoord, a continuing cohort study established in Ukraine in 2000.[7] HIV-positive pregnant women are enrolled at participating sites, and they and their children are prospectively followed up according to a standard protocol. Women identified as being infected with HIV before or during pregnancy or intrapartum and who deliver liveborn babies are eligible to enrol after giving informed consent. Linked data anonymised by use of study serial numbers are collected on study-specific questionnaires and include maternal sociodemographic, HIV-related, and delivery (mother and neonate) characteristics. Children are followed up to establish HIV infection status. The study protocol was approved by the Great Ormond Street Hospital for Children NHS Trust/Institute of Child Health Research Ethics Committee and by local institutional review boards.

Additionally we analysed data from an ECS substudy that enrolled women postnatally from 2007 to 2012, at five of seven ECS sites, to obtain longitudinal information after delivery. Initial postnatal data are collected at 3–6 months

post partum and are anonymously linked to the main study data with serial numbers. Data on variables relevant to the investigation of birth outcomes, including current smoking and maternal height, are collected.

In view of the increased risk of small size for gestational age and preterm delivery in women with multiple pregnancy,[11] we excluded 236 mother–infant pairs (115 twins and two triplet sets) from this analysis.

Definitions

Severity of maternal HIV was defined according to WHO Clinical Staging of HIV/AIDS. Maternal antenatal ART was classified as zidovudine monotherapy or combination ART (three or more antiretroviral drugs). History of injecting drug use at any time was based on self-report, clinical assessment, or presence of neonatal abstinence syndrome; we used history of injecting drug use rather than current use to reflect that drug use is a chronic and relapsing condition, and that drug use during pregnancy is likely to be substantially under-reported. Consumption of at least 20 cigarettes per day was classified as heavy smoking and of one to 19 cigarettes per day as moderate to light smoking. Caesarean section performed before rupture of membranes and onset of labour was deemed to be elective. Gestational age was reported to the nearest completed week, on the basis of ultrasonography findings (coverage of which is around 95% in the general antenatal population in Ukraine[18]) or last menstrual period if no scan was available. Preterm delivery was defined as that before 37 completed gestational weeks, and was classified as extreme (delivery at 31 completed weeks of gestation or earlier) or moderate or late (delivery at 32–36 completed weeks of gestation).[10] Low birthweight was defined as less than 2500 g. Babies were classified as being small for gestational age if birthweight for gestational age was lower than the tenth percentile, and severely small for gestational age if birthweight for gestational age was lower than the third percentile of the overall study population. Neonatal mortality was defined as death in the first 4 weeks of life. We created an individual-level social deprivation index[19] for the study by combining three variables: age at leaving full-time education, marital status, and having a sexual partner with a history of injecting drug use. We incorporated the latter factor to capture the social disadvantage found within populations of injecting drug users who are at high risk for HIV acquisition, and maternal injecting drug use was included in models separately as an important independent risk factor for adverse pregnancy outcomes.

Statistical analysis

Statistical analyses were done with R version 2.15.2 and Stata version 13.0. Because of the absence of population reference data to characterise small and severely small size for gestational age, we obtained percentiles for birthweight and gestational age by fitting the four-parameter Sinh-Arcsinh (SHASH) probability distribution in R to birthweights of the study population.[20] This distribution belongs to the class of generalised additive models for location, scale, and shape (GAMLSS), which allows specification of smooth linear predictors on each of the model's parameters.[21] We used natural cubic splines with degrees of freedom specified by minimising Akaike's information criterion. Models were fitted to obtain gender-specific percentiles of weight for gestational age. Final models were chosen according to the best approximation to the empirical third (severely small), and tenth (small) percentiles of size for gestational age.

We fitted Poisson regression models with robust SEs[22] to derive unadjusted and adjusted risk ratios (RRs) for incidence. Factors previously associated with preterm delivery, small size for gestational age, or both (ie, history of injecting drug use, social deprivation, parity, WHO HIV stage, antenatal ART, maternal age at delivery, smoking status, and maternal height[10,15]) and significantly associated ($p<0·05$) in univariable analyses were included in multivariable models, in which calendar time and centre were included as fixed effects. Associations between birth outcomes, smoking, and maternal height were assessed in women enrolled in the ECS main study and postnatal substudy. Multivariable models were based on complete-case analysis. We calculated p values for trend with logistic regression analyses with year used as a continuous variable.

Missing values for variables used to derive the social deprivation index were imputed with the 'mi' command in Stata, and correspondence analyses[23] were done in each of the ten imputed datasets. Sensitivity analyses were done with a non-imputed dataset. Weighted coordinates based on the percentage of inertia explained by the first and second correspondence analyses coordinates in each of the imputed datasets were averaged and included in cluster analyses that used *k*-means, which is a non-hierarchical method of defining groups. Use of three clusters minimised the Akaike's information criterion in multivariable models. Thus, the final social deprivation index was composed of three levels: least, more, and most deprived.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The study population comprised 8884 mothers who delivered liveborn singleton babies between January, 2000, and July, 2012. 2188 women also had data from the postnatal substudy. The median maternal age at delivery was 26·5 years (IQR 23·1–30·3), most women had WHO stage 1 HIV, and 54% were nulliparous (table 1). Almost all

	Number of women (%)
Maternal age (years; n=8863)	
≤17	140 (2%)
18–26	4587 (52%)
27–34	3475 (39%)
≥35	661 (8%)
WHO stage (n=7741)	
1	6444 (83%)
2	465 (6%)
3	734 (10%)
4	98 (1%)
Parity (n=8488)	
Nulliparous	4592 (54%)
Primiparous	2812 (33%)
Multiparous	1084 (13%)
Maternal ethnic origin (n=8824)	
White	8694 (99%)
Other	130 (1%)
Marital status (n=8680)	
Single	1388 (16%)
Married	3790 (44%)
Cohabiting	3502 (40%)
History of IDU (n=8760)	
Yes	1474 (17%)
No	7286 (83%)
Partner with a history of IDU (n=8623)	
Yes	2526 (29%)
No	6097 (71%)
Timing of HIV diagnosis (n=8392)	
Before pregnancy	2951 (35%)
First trimester	1623 (19%)
Second trimester	2291 (27%)
Third trimester	1217 (15%)
At delivery	310 (4%)
(Table 1 continues in next column)	
(Continued from previous column)	
Received ART during pregnancy (n=8856)	
Yes	7348 (83%)
No	1497 (17%)
Type of antenatal ART (n=8842)	
None	1497 (17%)
Zidovudine monotherapy	4396 (50%)
Combination ART	2949 (33%)
Timing of starting ART (n=7282)	
Before pregnancy	252 (4%)
First trimester	105 (1%)
Second trimester	3330 (46%)
Third trimester	3595 (49%)
Social deprivation index (n=8884)	
Least deprived	4141 (47%)
More deprived	2833 (32%)
Most deprived	1910 (22%)
Delivery mode (n=8824)	
Elective caesarean section	2619 (30%)
Emergency caesarean section	344 (4%)
Vaginal	5861 (66%)
Smoking status* (n=2078)	
Non-smoker	1175 (57%)
Light to moderate smoker	569 (27%)
Heavy smoker (≥20 cigarettes per day)	334 (16%)

IDU=injecting drug use. ART=antiretroviral therapy. *Available in the postnatal subgroup only.

***Table 1*: Maternal sociodemographic and clinical characteristics**

(8839 [99%] of 8851) women were born in Ukraine and 7292 (84%) of 8680 were married or cohabiting, nearly a third had a partner with a history of injecting drug use, and around a fifth of women were in the most socially deprived group (table 1). 1474 (17%) of 8760 women overall had a history of injecting drug use, but the proportion per year declined significantly from 2000 onwards, from 40% in 2000–01 to 10% in 2011 ($p_{trend}<0·0001$). In most women, HIV infection had been diagnosed during pregnancy and 83% received antenatal ART, mostly started in the third trimester (table 1), although with a shift towards starting earlier over the time period of the study: median gestational age at the start of ART initiation was 34 weeks (IQR 34–36) before 2005, 28 weeks (26–30) in 2005–08, and 24 weeks (22–28) in 2009–12 ($p_{trend}<0·0001$). The proportion of women who received no antenatal ART declined significantly from 78% in 2000, to 52% in 2001, to 9% in 2012 ($p_{trend}<0·0001$). Among the 2949 women who received combination ART, the type of regimen was available for 2911, of whom 2602 (89%) received a protease-inhibitor-based regimen (ritonavir-boosted lopinavir) with a zidovudine or lamivudine backbone; only 124 (4%) women received a regimen that included tenofovir.

Of the 8884 babies, 4474 (51%) were boys and two-thirds were delivered vaginally (table 1). Median birthweight was 3100 g (IQR 2750–3400) and 1092 (12%) infants were classified as having low birthweight. Median gestational age was 39 weeks (IQR 38–40). 780 (9%) of 8860 deliveries were preterm, with 107 (1%) being extreme preterm and 673 (8%) being moderate or late preterm. 94 (12%) of 780 born preterm were delivered by elective caesarean section at a median of 35 weeks' gestation (IQR 34–36) and 86 (11%) by emergency caesarean section. 889 (10%) of 8788 infants were classified as being small for gestational age, among whom 260 (29%) were severely small. 77 (10%) of 780 preterm infants had small size for gestational age, as did 812 (10%) of 8016 term babies. 77 (9%) of 889 infants who were small weight for gestational age were delivered preterm.

In univariable analyses, which included 7329 women, factors associated with increased risk of preterm delivery were WHO stage 4 HIV, no antenatal ART or antenatal

combination ART (*vs* zidovudine monotherapy), history of injecting drug use, being in the most socially deprived group, parity, and older maternal age (table 2). In multivariable analyses, no antenatal ART and WHO stage 4 HIV were each associated with risk of preterm delivery increased by around two times (table 2). Positive associations were seen between risk of preterm delivery and history of injecting drug use, social deprivation, WHO stage 3, combination ART use (*vs* zidovudine monotherapy), increasing calendar time, and older maternal age that persisted after adjustment for other variables (table 2). In a multivariable model that excluded the 94 deliveries by elective caesarean section before 37 weeks' gestation, calendar time was no longer associated with preterm delivery (adjusted RR 1·03, 95% CI 0·99–1·06, p=0·12), but other associations remained broadly similar.

Monitoring of CD4 cell counts was not available in the earlier years of the study and is not included in our main multivariable model. Nevertheless, analysis of a subgroup of 3119 women who had antenatal CD4 cell counts available and delivered from 2008 onwards showed that high CD4 cell counts were associated with reduced risk of preterm delivery (adjusted RR 0·64, 95% CI 0·47–0·87 for CD4 cell counts of 351–500 cells per mL *vs* 350 cells per mL or lower, and 0·73, 0·55–0·96 for CD4 cell counts of 500 cells per mL or higher *vs* 350 cells per mL or lower) after adjustment for all other variables in the main multivariable model, apart from WHO HIV stage. The association between combination ART and preterm delivery remained after adjustment for CD4 cell count (adjusted RR 1·40, 95% CI 1·02–1·93, p=0·04).

In the postnatal substudy, heavy and moderate smoking were associated with increased risk of preterm delivery in univariable analyses of 1662 women (RR 2·55, 95% CI 1·79–3·65 and 1·51, 1·03–2·19, respectively, *vs* non-smokers). In a multivariable model that included smoking plus the variables included in the main adjusted model, heavy smoking and history of injecting drug use were associated with increased risk of preterm delivery (adjusted RR 2·16, 95% CI 1·34–3·49 and 2·06, 1·40–3·03, respectively). The association between preterm delivery and history of injecting drug use was weakened after adjustment for smoking, from adjusted RR 2·55 (95% CI 1·78–3·67) to 2·06 (1·40–3·03), as was the association between preterm delivery and being in the most deprived group, from 1·35 (0·87–2·08) to 1·18 (0·77–1·82).

In univariable analyses injecting drug use, being in the most deprived group, higher WHO HIV stage, no ART or combination ART (compared with zidovudine monotherapy), and age greater than 35 years were associated with risk of small size for gestational age (table 3). In the multivariable analysis, factors that remained significantly associated with risk of small size for gestational age were antenatal combination ART, no antenatal ART, history of injecting drug use, and being in the most socially deprived group (table 3).

	Risk ratio (95% CI)	Adjusted risk ratio* (95% CI)	p value
History of IDU			
Yes *vs* no	2·30 (1·97–2·69)†	1·64 (1·38–1·95)	<0·0001
Social deprivation index			
More *vs* least deprived	1·16 (0·98–1·40)	1·19 (0·99–1·44)	0·07
Most *vs* least deprived	1·51 (1·27–1·81)†	1·38 (1·11–1·71)	0·004
Parity			
1 *vs* 0	1·22 (1·04–1·44)†	0·97 (0·82–1·15)	0·7
≥2 *vs* 0	1·53 (1·24–1·88)†	1·01 (0·81–1·27)	0·9
WHO HIV stage			
2 *vs* 1	1·02 (0·73–1·42)	0·85 (0·60–1·21)	0·37
3 *vs* 1	1·66 (1·35–2·04)†	1·32 (1·06–1·65)	0·015
4 *vs* 1	3·69 (2·59–5·26)†	2·42 (1·71–3·41)	<0·0001
Antenatal ART			
None *vs* zidovudine monotherapy	3·45 (2·88–4·14)†	2·94 (2·43–3·57)	<0·0001
Combination ART *vs* zidovudine monotherapy	1·75 (1·46–2·10)†	1·40 (1·14–1·73)	0·001
Calendar time per additional year	1·02 (1·00–1·05)	1·04 (1·01–1·07)	0·009
Maternal age (years)			
≤17 *vs* 18–26	0·90 (0·43–1·86)	0·84 (0·42–1·71)	0·650
27–34 *vs* 18–26	1·50 (1·28–1·76)†	1·28 (1·08–1·51)	0·003
≥35 *vs* 18–26	1·97 (1·55–2·51)†	1·55 (1·20–1·99)	0·001

IDU=injecting drug use. ART=antiretroviral therapy. *Adjusted for study centre, antenatal ART, history of IDU, social deprivation index, parity, WHO HIV stage, maternal age, and calendar time. †Significant in the univariable analysis.

***Table 2*: Risk factors for preterm delivery in 7328 women**

	Risk ratio (95% CI)	Adjusted risk ratio* (95% CI)	p value
History of IDU			
Yes *vs* no	1·57 (1·35–1·83)†	1·39 (1·16–1·65)	<0·0001
Social deprivation index			
More *vs* least deprived	1·13 (0·97–1·34)	1·13 (0·96–1·34)	0·15
Most *vs* least deprived	1·39 (1·17–1·63)†	1·32 (1·09–1·61)	0·006
WHO HIV stage			
2 *vs* 1	1·02 (0·76–1·36)	0·96 (0·71–1·31)	0·8
3 *vs* 1	1·28 (1·04–1·58)†	1·12 (0·89–1·40)	0·3
4 *vs* 1	1·73 (1·08–2·76)†	1·46 (0·90–2·37)	0·1
Antenatal ART			
None *vs* zidovudine monotherapy	1·87 (1·56–2·23)†	1·60 (1·32–1·94)	<0·0001
Combination ART *vs* zidovudine monotherapy	1·43 (1·23–1·66)†	1·33 (1·12–1·60)	0·002
Calendar time per additional year	1·02 (0·99–1·04)	1·01 (0·98–1·04)	0·5
Maternal age (years)			
≤17 *vs* 18–26	0·74 (0·38–1·46)	0·71 (0·36–1·39)	0·3
27–34 *vs* 18–26	1·12 (0·98–1·30)	1·03 (0·89–1·19)	0·7
≥35 *vs* 18–26	1·35 (1·07–1·72)†	1·18 (0·93–1·50)	0·2

IDU=injecting drug use. ART=antiretroviral therapy. *Adjusted for study centre, antenatal ART, history of IDU, social deprivation index, parity, WHO HIV stage, maternal age, and calendar time. †Significant in the univariable analysis.

***Table 3*: Risk factors for delivery of babies with small size for gestation age in 7581 women**

Among women enrolled in the postnatal substudy, only current heavy smoking was associated with an increased risk of small size for gestational age (n=1515; RR 1·64,

95% CI 1·12–2·40), but not moderate smoking (1·21, 0·82–1·79). Taller maternal height was associated with decreased risk of small size for gestational age (RR 0·97, 95% CI 0·95–1·00, p=0·04 per additional 5 cm). After adjustment for the other variables in the main model, the association between height and small size for gestational age remained (adjusted RR 0·97, 95% CI 0·94–1·00, p=0·030, per additional 5 cm) and the associations with history of injecting drug use (1·24, 0·78–1·98) and current heavy smoking (1·58, 0·94–2·66) were lost.

Birth outcomes were assessed in 2559 women who received antenatal combination ART with one nucleoside reverse transcriptase inhibitor backbone throughout pregnancy. After adjustment for factors in table 3, risk of preterm delivery, small size for gestational age, and low birthweight in the 123 women who received tenofovir were not significantly greater than in the 2204 taking zidovudine or lamivudine (adjusted RR 0·83 95% CI 0·38–1·79 *vs* 1·15, 0·66–2·02 or 1·09, 0·65–1·82). Statistical power for this analysis, however, was limited due to the small number of women who received tenofovir.

The sensitivity analyses involved 7581 women. Increased risk of severe small size for gestational age was associated with no antenatal ART (adjusted RR 1·96, 95% CI 1·32–2·90), antenatal combination ART (1·52, 1·08–2·12), and history of injecting drug use (1·64, 1·17–2·31). For the 2078 women with information on smoking status, heavy smoking was associated with increased risk of severe small size for gestational age (RR 2·14, 95% CI 1·05–4·36), but no associations were seen with moderate smoking (1·69, 0·85–3·33) or maternal height (1·00, 0·95–1·05 per additional 5 cm). 41 (0·5%) of 8884 neonates died, yielding neonatal mortality of 4·62 per 1000 (95% CI 3·31–6·26). Of these 41 neonates, 20 (49%) were preterm (eight extreme, 12 moderate or late), and five (13%) were small for gestational age. The RR for neonatal death was 9·9 (95% CI 5·4–18·1) for preterm delivery and 1·27 (0·50–3·23) for small size for gestational age. Multiple imputations were shown to change the effect of social deprivation on preterm delivery outcome by 12% for more deprived versus least deprived and by 5% for most deprived versus least deprived. Changes in the effect on small size for gestational age were around 10% for more deprived and 13% for most deprived versus least deprived. All estimates were consistent with those after multiple imputations in the direction of the effect.

Discussion

In this cohort of HIV-positive pregnant women delivering in Ukraine in 2000–12, preterm delivery was seen in 9%. The limited overlap between these and the 10% of infants who were small for gestational age is consistent with the difference in causes underlying duration of pregnancy and restriction in fetal growth. The cumulative prevalence of small size for gestational age and preterm delivery was 18%. During the study period, history of injecting drug use declined significantly, and coverage with antenatal ART, particularly with combination ART,[9] increased.

Rates of preterm delivery vary between and within populations, with estimates of around 6% in Europe, 11% in North America, 9% in Asia, and 12% in Africa.[24] Information on rates in Ukraine and eastern Europe, however, is scarce. 5·2% of births were preterm in around 3000 births in urban Ukraine in 1992–95 (85% of which were spontaneous)[25] and rates in Russia range from 8·7% among 17 000 births in Murmansk in 2006–07[26] to 12·4% of all deliveries in Tula Oblast in 2000.[27] With respect to HIV-positive women, our overall rate of 9% for preterm delivery is lower than that reported from studies in Russia (25% in 2004–08),[28] France (14% in 2000–09),[29] the UK (13% in 1990–2005), Latin America (20% in 2002–12),[30] and the USA (20% in 2008–10),[16] which reflects differences in background rates and characteristics of study populations.

We explored history of injecting drug use rather than current use because it is a chronic and recurring condition. In our cohort, women with a history mainly injected homemade opiates.[31] In the main adjusted models, history of injecting drug use was associated with increased risks of preterm delivery and small size for gestational age. These findings are consistent with those of other studies of HIV-positive[15,28,29] and HIV-negative women, and emphasises the need for a comprehensive package of care that includes opioid-substitution therapy.[31] The prevalence of smoking in this study was higher than reported in a survey of women of reproductive age in Ukraine in 2008–10 (43% *vs* 18% overall and 23% among women aged 25–34 years).[32] Smoking prevalence is generally increased among people living with HIV, including pregnant women,[14,33] but the rate in our study was still higher than in other studies of HIV-positive pregnant women: 20% in western Europe, 25% in Latin America, and 14–17% in the USA.[14,16,30,33] Nevertheless, we did not have data on smoking during pregnancy and used data on self-reported postnatal smoking as a proxy for antenatal tobacco exposure. Prevalence of smoking during pregnancy, therefore, might have been overestimated. In a subanalysis that included smoking and maternal height, the 16% of women with heavy smoking had a significantly increased risk of preterm delivery, which is consistent with previous findings on smoking being associated with shortened gestation in general[11] and in HIV-positive populations.[33]

Maternal WHO stage 4 HIV disease was associated with increased risk of preterm delivery but not with small size for gestational age. This finding supports those of previous studies that have associated symptomatic HIV disease, AIDS, or severe immunodeficiency with increased risk of preterm delivery.[15,16,29]

The associations between antenatal ART and adverse birth outcomes need careful interpretation in view of the changing clinical practices over the study period. The Ukraine national policy for prevention of mother-to-child

transmission changed from use of zidovudine, single-dose nevirapine, or both, to combination ART (predominantly based on boosted protease inhibitors).[7,9] Although we adjusted for WHO HIV stage and calendar time, we had limited ability to adjust for confounding by indication for ART during pregnancy in our main analyses because we could not adjust for CD4 cell counts, owing to data not being routinely available and delivered until after 2008, and because reasons for prescription of antenatal combination ART have changed over time.[9] When antenatal CD4 cell count was included, antenatal combination ART remained associated with preterm delivery, but some of the increased risk might have been due to residual confounding caused by more severe HIV disease in this group. The significant association between no antenatal ART and preterm delivery (adjusted RR 2·94, 95% CI 2·43–3·57) might be partly explained by women delivering before having the opportunity to start ART. Nevertheless, a correlation between no ART and lack of or late presentation for antenatal care is likely, and this is a well known risk factor for preterm delivery and small size for gestational age.[34] Our findings of an increased risk of preterm delivery and small size for gestation age associated with combination ART versus zidovudine monotherapy (table 2) are consistent with those in other studies.[14–17] Preliminary data from the PROMISE trial[35] indicated that pregnancy outcomes were more severe among infants exposed to tenofovir, emtricitabine, and ritonavir-boosted lopinavir than among those exposed to zidovudine, lamivudine, and ritonavir-boosted lopinavir. We detected no increase in the risks of preterm delivery, small size for gestational age, or low birthweight among the small number of women who received antenatal combination ART containing tenofovir, but statistical power for this assessment was limited. Evidence is growing of increased risks of preterm delivery in women who conceive while taking combination ART or who start combination ART during pregnancy, although the mechanisms are potentially different.[16,29,30] We plan to assess outcomes focusing on timing and type of combination ART, particularly in view of the expanding use of combination regimens in Ukraine.[9]

Median neonatal mortality was 4·62 per 1000 livebirths, which is similar to the 2014 Ukraine national estimate of 5·0 per 1000.[6] Our rate seems to be similar to that in Latin America (4·0 per 1000 livebirths), another lower-middle-income region,[30] and slightly higher than the rate in the UK (3·6 per 1000).[36] Preterm delivery is the main cause of neonatal mortality worldwide, and half the neonatal deaths in this study were in preterm infants.

Our study is limited by the potential for confounding and bias, including social desirability bias (eg, in relation to reporting of injecting drug use and smoking). We did not collect data on hypertension, sexually transmitted infections, previous preterm delivery, second-hand smoke exposure, alcohol use, timing of the start of antenatal care, and psychosocial stressors, which are known risk factors for poor birth outcomes. We also did not obtain data on a comprehensive range of socioeconomic indicators, such as employment and housing status, for inclusion in the social deprivation index. The ECS enrols around 30% of all HIV-positive women delivering nationally in Ukraine, and findings are expected to be generalisable to this population. Our inclusion of the social deprivation index strengthens the study in view of the associations between social deprivation and adverse pregnancy outcomes.

In this study we identified several risk factors for preterm delivery and small size for gestational age in mothers infected with HIV. Some were directly related to HIV infection, such as poor clinical status, and others were shared with the general antenatal population, such as substance use and social deprivation. Around 4000 babies are born to HIV-positive women in Ukraine annually.[2] On the basis of our findings, we estimated that roughly 720 infants born to HIV-positive women per year at the end of the study period will be preterm, have small size for gestation age, or both, and that 18 will die in the neonatal period. 80–160 infants will be infected with HIV, of whom around a fifth will be preterm, if based on the current mother-to-child transmission rates of 2–4%,[2,9] although the numbers will decrease as use of antenatal combination ART increases. Elimination of new HIV infection in infants is an important issue in Europe and worldwide.[1] Our findings indicate the importance of ensuring that continuing efforts to improve perinatal outcomes in Ukraine in general are extended to HIV-positive women. As antenatal combination ART has been available in programmes to prevent mother-to-child transmission since 2007, the association between this approach and preterm delivery in this population requires further research and monitoring of pregnancy outcomes as use increases.

Contributors

RM and CT contributed to the design of the study and of the postnatal substudy. RM and AV contributed to the acquisition of data. All authors contributed to developing the concept of the Article and interpreted the results. EB did and MC-B contributed to the statistical analysis. All authors were involved in drafting and revising the intellectual content of the paper and read and approved the final manuscript.

Ukraine European Collaborative Study Group

T Pilipenko, Perinatal Prevention of AIDS Initiative, Odessa, Ukraine; S Posokhova, Regional Hospital, Odessa, Ukraine; Y Barishnikova, T Kaleeva, S Servetsky, and R Tereshenko, Odessa Regional Centre for HIV/AIDS, Ukraine; M P Grazhdanov, E Kulakovskaya, and S Solokha, Donetsk Regional Centre for HIV/AIDS, Ukraine; I Adejnova, I Raus, and O V Yurchenko, Kiev City Centre for HIV/AIDS, Ukraine; O Govorun, I Kochergina, L Ostrovskaya, and Z Ruban, Mikolaiv Regional Centre for HIV/AIDS, Ukraine; G Kruglenko, L Kvasha, and N Primak, Kriviy Rig City Center for HIV/AIDS, Ukraine; E Dotsenko, G Kiseleva, A Stelmah, and O A Zalata, Crimean Republic Centre for HIV/AIDS, Ukraine, N Bashkatova, and V Gigil, Mariupol AIDS Centre, Ukraine.

Declaration of interests

CLT has received speaker's fees from Biotest AG. CT received a grant from AbbVie for a pharmacovigilance study on use of Kaletra in pregnancy in the UK. The other authors declare no competing interests.

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See Online for appendix

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