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Authors: Emmanouil BAGKERIS[1], Ruslan MALYUTA, Alla VOLOKHA, Mario CORTINA-BORJA[1], Heather BAILEY[1], Claire TOWNSEND[1], Claire THORNE[1] for the Ukraine European Collaborative Study in EuroCoord

Full title: Pregnancy outcomes in an observational cohort study of HIV-positive women in Ukraine, 2000-2012

Affiliations:[1] Population, Policy and Practice Programme, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, [2]Perinatal Prevention of AIDS Initiative, Odessa, Ukraine, [3] Shupyk National Medical Academy of Postgraduate Education, Kiev, Ukraine.

Corresponding author: Claire Thorne, Population, Policy and Practice Programme, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, Tel: (+44) 2079052105, email: claire.thorne@ucl.ac.uk

Abstract

Background: Observational prospective cohort study of HIV-positive pregnant women and their infants in Ukraine.

Methods: HIV-positive pregnant women diagnosed before/during pregnancy (including intrapartum) and delivering liveborn infants are eligible for enrolment in the European Collaborative Study, which enrols approximately 30% of all HIV-positive women delivering in Ukraine at seven sites. Data on 8884 HIV-positive mother/liveborn infant pairs delivering from 2000-2012 were analysed. Poisson regression models were fitted to identify factors associated with preterm delivery (PTD, <37 weeks gestation), and small-for-gestational-age (SGA, below 10th percentile of birthweight-for-gestational-age).

Findings: Median maternal age was 26·5 years (IQR 23·1-30·3), 10.7% had WHO stage 3/4 disease and 16·8% had an injecting drug use (IDU) history. PTD prevalence was 8·8% (780/8860, 95%CI 8·2-9·4) overall and 8·7% (77/889, 95%CI 6·9-10·7) among SGA infants. Factors associated with PTD were IDU history (Adjusted Incidence Risk Ratio (AIRR) 1·64, 95%CI 1·38-1·95), non-receipt of antenatal antiretroviral therapy (ART) or receipt of combination ART (cART) (vs. zidovudine monotherapy, AIRR 2·94 95%CI 2·43-3·57 and 1·41 95%CI 1·14-1·73), WHO stage 4 HIV disease (vs. stage 1, AIRR 2·42, 95%CI 1·71-3·41) and social deprivation (AIRR 1·38 95%CI 1·11-1·71 for most vs. least deprived groups). IDU history and social deprivation were associated with SGA (AIRR 1·39 95%CI 1·16-1·65 and 1·32 95%CI 1·09-1·61), as was non-receipt of ART or receipt of cART (1·60 95%CI 1·32-1·94 and 1·33 95%CI 1·12-1·60). Neonatal mortality rate was 4·62/1000; of 41 deceased neonates, 20 were preterm.

Interpretation: Risk factors included HIV-specific (e.g. worse clinical status) factors and others shared by the general antenatal population (e.g. substance use). Findings highlight the importance of monitoring pregnancy outcomes in Ukraine, given increasing use of antenatal cART.

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Key Words: preterm birth; small for gestational age; antiretroviral therapy; pregnancy; social deprivation; Ukraine.

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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 (IDU) has driven the HIV epidemic in this region, heterosexual acquisition became the main transmission route in newly diagnosed individuals in Ukraine in 2008 and of 21,631 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 50,000 people were receiving antiretroviral therapy (ART)[4] by 2013, around half the total estimated to have treatment indications according to WHO 2010 guidelines[1].

In the general population in Ukraine, the maternal mortality rate is 25 per 100,000, and the infant mortality rate is 9 per 1000 live-births, with 75% of pregnant women having at least four antenatal care visits[5, 6]. Prevention of mother-to-child transmission (PMTCT) of HIV programmes started in 2001 and included universal antenatal HIV testing and repeat testing in the third trimester, short-course zidovudine monotherapy (ZDVm) and/or single dose nevirapine and provision of free infant formula [7, 8]. Subsequently ZDVm was recommended from at least 28 weeks gestation, and by 2007 the MTCT rate had fallen to around 7%[7]; in that year Ukraine adopted the World Health Organization (WHO) Option B strategy (triple combination antiretroviral therapy (ART) for all pregnant women regardless of clinical or immunological status)[9]. Current MTCT rates are 2-4%.[2, 9] National guidelines recommend elective caesarean delivery for HIV-positive women with a viral load >1000 copies/ml but access to viral load monitoring has been limited,[3] with substantial variation in mode of delivery between clinical centres[7].

Adverse birth outcomes such as low birth weight (LBW), preterm delivery (PTD) and small-for-gestational-age (SGA) have multiple aetiologies which are not well understood[10]. Associated risk factors include short maternal height, low/high body mass index, uterine/placental abnormalities, illicit drug use, lower socioeconomic status (SES), smoking, unintended pregnancy, psycho-social stress, prior PTD, infections and multiple pregnancy[10, 11]. Some, but not all studies, have identified maternal HIV infection as a risk factor for PTD, LBW, and poor fetal growth, with greatest risk for those with symptomatic disease, or severe immunodeficiency[12-14]. Antenatal combination ART (cART) has been associated with increased risk of PTD in HIV-positive women in studies in Europe, the US and Africa[14-17], whilst other studies found no association.

Pregnancy outcomes other than vertical HIV transmission have not yet been investigated in HIV-positive women in Ukraine, but characterisation of these outcomes over the course of the epidemic so far is important for identifying health priorities and for future work exploring the impact of specific PMTCT interventions. Here, we describe birth outcomes in a cohort of HIV-positive women delivering over a thirteen-year period and investigate risk factors for adverse birth outcomes.

Materials and Methods

The European Collaborative Study (ECS) in EuroCoord (www.EuroCoord.net) is a cohort study, established in Ukraine in 2000[7], in which HIV-infected pregnant women are enrolled and their infants prospectively followed according to a standard protocol. Women identified as HIV-infected before/during pregnancy or intrapartum and delivering a live-born infant are eligible to enrol with informed consent; linked anonymised data are collected on study-specific questionnaires, using study serial numbers. Information collected includes maternal socio-demographic and HIV-related characteristics, and delivery/infant characteristics. Infants are followed up to establish infection status.

A sub-study was established to obtain longitudinal information on HIV-positive women after delivery: women were enrolled in five of the seven Ukraine ECS sites from December 2007 to 2012, with initial postnatal data collected around 3-6 months postpartum. Data are anonymously linked to ECS data using study serial numbers. Variables collected relevant to investigation of birth outcomes included current smoking, and maternal height.

Given increased risk of SGA and PTD in multiple pregnancies[11], 236 mother-infant pairs from 117 multiple pregnancies (115 twin pairs, 2 triplet sets) were excluded from analyses. The study population for this analysis was 8884 ECS mother-infant pairs, delivering to August 2012, of whom 2188 women were also in the postnatal sub-study.

Definitions

Maternal HIV symptoms were reported according to WHO clinical staging. Maternal antenatal ART was categorised as ZDVm or cART (defined as ≥3 antiretroviral drugs). IDU history (use of injecting drugs at any time) was determined by self-report, clinical assessment, or presence of neonatal abstinence syndrome; we used IDU history (rather than current IDU) for all analyses to reflect that drug use is a chronic and relapsing condition, and that drug use during pregnancy is likely to be substantially under-reported. Heavy and light-moderate smoking were defined as ≥20 and 1-19 cigarettes/day, respectively. Elective caesarean sections (CS) were those before rupture of membranes and onset of labour. Gestational age was reported to the nearest completed week based on ultrasound (coverage of which is around 95% in the general antenatal population in Ukraine[18]) or, if no ultrasound, last menstrual period. PTD was defined as delivery before 37 completed gestational weeks; extreme/severe PTD as delivery at ≤31 completed weeks of gestation, and moderate/late PTD as 32-36 completed weeks[10]. LBW was defined as birthweight <2500g. Infants were considered to be SGA if <10th percentile of birthweight-for-gestational age, and severely SGA if <3rd percentile. Neonatal mortality was defined as death in the first four weeks of life. An individual Social Deprivation Index (SDI)[19] was created by combining three variables (age at leaving full-time education, marital status, and history of a sexual partner who injected drugs 'IDU partner'). IDU partner was incorporated within the SDI to capture social disadvantage found among populations of IDUs at high risk for HIV acquisition, while maternal IDU was included in models separately as an important independent risk factor for adverse pregnancy outcomes.

Statistical analysis

Due to the lack of population reference data to characterise SGA and severely SGA, we obtained percentiles for weight and gestational age based on fitting the 4-parameter Sinh-Arcsinh (SHASH) probability distribution to birthweights of the study population of 8884 mother-infant pairs[20]. This distribution belongs to the class of generalised additive models for location, scale, and shape (GAMLSS) which allows specifying 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 (AIC). Models were fitted to obtain gender-specific centiles of weight-for-gestational-age. Final models were chosen based on the best approximation to the empirical 3rd (severe SGA), and 10th (SGA) percentiles.

Given the relatively high prevalence of study outcomes, Poisson regression models with robust standard errors[22] were fitted to derive unadjusted and adjusted incidence rate ratios (AIRR) in analyses. Factors previously found to be associated with the outcomes i.e. IDU history, social deprivation, parity, WHO stage, antenatal ART, maternal age at delivery, smoking status, and maternal height[10, 15] and associated (p <0·05) with PTD and/or SGA in univariable analyses were included in multivariable models, plus calendar time and centre as fixed effects. Associations between birth outcomes, smoking, and maternal height were assessed in a sub-analysis using data on a subgroup of women enrolled in both the ECS and the postnatal cohort study. Multivariable models were based on complete-case analysis.

Missing values of the variables defining the SDI were imputed using the `mi` command in STATA and then correspondence analyses (CA)[23] were performed in each of the ten imputed datasets. Sensitivity analyses were conducted using a non-imputed dataset. Weighted coordinates based on the percentage of inertia explained by the first and second CA coordinates in each of the imputed datasets were averaged and included in cluster analyses using *k*-means, which is a non-hierarchical method of defining groups. Use of three clusters minimised the AIC in multivariable models. Thus the final SDI was composed of three levels: least, more, and most deprived. Statistical analyses were conducted using R, version 2.15.2 (R Foundation for Statistical Computing, Vienna) and STATA version 13.0 (StataCorp, College Station, Texas).

Role of funding source

The sponsor 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

Cohort characteristics

Of 8884 mother-child pairs enrolled in the ECS in 2000-2012, median maternal age at delivery was 26·5 years, most women had WHO stage I disease, and 54% were nulliparous (Table 1). Almost all women were born in Ukraine (99·5%, 8839/8851), 84·0% (7292/8680) were married/cohabiting, and 29·3% (2526/8623) had an IDU partner. Overall 16·8% (1474/8760) of women had an IDU history, significantly declining from 40·4% (21/52) in 2000/01 to 26·8% (64/239) in 2002/03, 14% (180/1287) in 2008/09, and 10% (110/1095) in 2011/12 ($\chi^2_{12\text{trend}}$=221·7, p<0·0001). Around one-third (2951/8392) had been diagnosed as HIV-positive pre-pregnancy, 61·1% (5131/8392) during pregnancy, and 3·7% (310/8392) at delivery. Overall 83·1% of women received antenatal ART, mostly initiated in the third trimester, although with a shift to earlier initiation over time: median gestational age at ART initiation was 34 weeks (IQR: 34-36) before 2005, 28 weeks (IQR: 26-30) in 2005-2008, and 24 weeks (IQR: 22-28) in 2009-2012. The proportion of women receiving no antenatal ART declined significantly from 78% in 2000 to 52% in 2001 to 9% in 2012. Among the 2949 women receiving cART, type of regimen was available for 2911 of whom most (89%, 2602) received a PI-based regimen (mainly lopinavir/ritonavir) with a zidovudine(ZDV)/lamivudine backbone; only 124 women received a tenofovir-containing regimen. Regarding the SDI, around one-fifth of women were in the most deprived group (Table 1).

Delivery characteristics and prevalence of PTD and SGA

Of the 8884 singleton infants, 4474 (50·8%) were male and two-thirds were delivered vaginally (Table 1). Median birthweight was 3100g (interquartile range (IQR): 2750-3400) and 1092 (12·3%) infants were LBW. Median gestational age was 39 weeks (IQR 38-40) and 8·8% of deliveries (780/8860) were preterm, with 1·2% (*n*=107) extreme/severe preterm and 7·6% (*n*=673) moderate/late preterm. Prevalence of SGA was 10·1% (889/8788); 9·9% (77/780) among preterm infants and 10·3% (812/8016) among term infants. Among all SGA infants, 29·3% (260/889) were severely growth restricted (<3rd percentile) and 8·7% (77/889) were preterm. Among the 780 PTDs, 94 (12·2%) were delivered by elective CS (median, 35 gestational weeks) and 86 (11·2%) by emergency CS.

Risk factors for PTD

In univariable analyses (*n*=7329), factors associated with increased risk of PTD were WHO Stage 4, non-receipt of antenatal ART or receipt of cART (versus ZDVm), IDU history, being in the most socially deprived group, parity, and older age (Table 2). In multivariable analyses, non-receipt of antenatal ART and WHO stage 4 were each associated with a more than two-fold increased risk of PTD. The positive associations between PTD risk and IDU history, social deprivation, WHO stage 3 (vs WHO stage 1), cART use (vs ZDVm), increasing calendar time, and older maternal age also persisted after adjustment for other variables (Table 2). In a multivariable model excluding the 94 deliveries by elective CS at <37 weeks from the study population, calendar time was no longer associated with PTD (AIRR 1·03 95%CI 0·99-1·06, *p*=0·117), but other associations remained broadly the same.

CD4 monitoring was not available in the earlier years of the study and is not included in our main multivariable model. However in a sub-analysis of 3119 women with an antenatal CD4 count available who delivered from 2008 onwards, those with a higher CD4 count had a lower risk of PTD (AIRR 0·64, 95%CI 0·47-0·87 for CD4 count 351-500 cells/mm^3 versus ≤350) and (AIRR 0·73, 95%CI 0·55-0·96 for CD4≥500 cells/mm^3 versus ≤350) after adjusting for all other variables in the main multivariable model apart from WHO stage. The association between cART and PTD remained after adjusting for CD4 count (AIRR 1·40, 95%CI 1·02-1·93, *p*=0·035).

In the sub-analysis of women in the postnatal cohort in addition to the ECS (*n*=1662), heavy smoking as well as moderate smoking were associated with increased risk of PTD in univariable analyses (IRR 2·55, 95%CI 1·79-3·65, *p*<0·0001 and IRR 1·51, 95%CI 1·03-2·19, *p*=0.033 respectively versus non-smokers). In a multivariable model which included smoking plus the variables included in the main adjusted model, heavy smoking (vs. non-smoking), and IDU history were associated with a two-fold increased risk of PTD (AIRR 2·16, 95%CI 1·34-3·49, *p*=0·002 and 2·06 (95%CI 1·40-3·03, *p*<0·0001 respectively). There was an attenuation of the association between PTD and IDU after adjusting for smoking from AIRR 2·55, 95%CI 1·78-3·67 to 2·06, 95%CI 1·40-3·03, and in the association between PTD and SDI (most deprived) from AIRR 1·35, 95%CI 0·87-2·08 to 1·18, 95%CI 0·77-1·82 (vs least deprived group).

Risk factors for SGA

Factors associated with significantly increased risk of having an SGA infant in univariable analyses (*n*=7581) are shown in Table 3. In the multivariable analysis, factors remaining significantly associated with increased SGA risk were antenatal cART, and non-receipt of antenatal ART (vs. ZDVm), IDU history and being in the most deprived SDI group, after adjusting also for WHO stage, calendar time, maternal age, and study centre (Table 3).

In the sub-analysis of women enrolled in the postnatal cohort (*n*=1515), only current heavy smoking and not moderate smoking was associated with an increased risk of SGA (IRR 1·64, 95%CI 1·12-2·40, *p*=0·011 vs. non-smokers and 1·21 (0·82-1·79), *p*=0·334 respectively), while taller maternal height was associated with decreased risk (IRR 0·97, *p*=0·042 per additional 5cm). After adjusting for the other variables in the main model, there was a decreased risk of SGA for taller women (AIRR 0·97, 95%CI 0·94-1·00, *p*=0·030 per additional 5cm), while IDU history and current heavy smoking were no longer associated with increased SGA risk (AIRR 1·24, 95%CI 0·78-1·98, *p*=0·358 and AIRR 1·58, 95%CI 0·94-2·66, *p*=0·087 respectively).

In a second SGA sub-analysis examining birth outcomes among 2559 women who started cART during pregnancy and received one NRTI backbone throughout, those who received tenofovir (n=123) did not have a significantly increased risk of PTD, SGA or LBW compared with those on ZDV/lamivudine (n=2204) (AIRR 0·83 95%CI 0·38-1·79, AIRR 1·15 95%CI 0·66-2·02 and AIRR 1·09 95%CI 0·65-1·82 respectively, adjusted for factors in Table 3); however, statistical power was limited due to the small number of women who received tenofovir.

In a sensitivity analysis for severe SGA (third percentile) (n=7581), receipt of no antenatal ART or antenatal cART (vs ZDVm) and IDU history were associated with increased risk of severe SGA (AIRR 1·96, 95%CI 1·32-2·90, *p*=0·001 vs. ZDVm; AIRR 1·52, 95% CI 1·08-2·12, *p*=0·014 vs. ZDVm and AIRR 1·64, 95%CI 1·17-2·31, *p*=0.005 vs. non-IDU, respectively). For the women with information on smoking status, heavy smoking was associated with increased risk of severe SGA (IRR 2·14, 95%CI 1·05-4·36, *p*=0.036). However, moderate smoking and maternal height were not associated with risk of severe SGA (IRR 1·69, 95%CI 0·85-3·33 vs. non-smoking, *p*=0·133 and IRR 1·00, 95%CI 0·95-1·05 per additional 5cm, *p*=0·980 respectively).

Neonatal mortality

The neonatal mortality rate was 4·62 per 1000 (41/8884, 95% CI 3·31-6·26) overall. Of the 41 neonates who died, 20 (48·8%) were delivered preterm (8 extreme/severe preterm, 12 moderate/late preterm), and five (12·5%) were SGA. The risk ratio for neonatal death was 9·9 (95% CI 5·4-18·1) for preterm versus term delivery and 1·27 (95% CI 0·50-3·23) for SGA versus appropriate weight for gestational age.

Sensitivity analysis for the multiple imputation

Results from the sensitivity analysis conducted to evaluate the effect of imputation of missing data on SDI indicated that for the PTD outcome there was a 12% change for the more vs. least deprived estimate and a 4.5% change of the estimate for the most vs. least deprived after the multiple imputation. For the SGA outcome the change of the estimates was around 10% and 13% for the more vs. least deprived group and the most vs. least deprived group respectively. All estimates were consistent with the `mi` analysis in the direction of the effect.

Discussion

In this cohort of HIV-positive pregnant women delivering in Ukraine in 2000-2012, 9% delivered preterm. The limited overlap between these and the 10% of infants who were SGA is consistent with largely separate aetiologies for duration of pregnancy and fetal growth restriction. Cumulative prevalence of SGA and PTD reached 17·9% overall. Over this period, IDU has declined and coverage with antenatal ART has increased, particularly cART[9], and we have documented a significant increase in PTD.

Rates of PTD 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 PTD rates in Ukraine and Eastern Europe is scarce: a PTD rate of 5·2% was reported in around 3000 births in urban Ukraine in 1992-95 (85% spontaneous)[25], while in Russia PTD rates range from 8·7% among 17,000 births in Murmansk in 2006-2007[26] to 12·4% among all deliveries in Tula oblast in 2000[27]. With respect to HIV-positive women, the overall PTD rate here (9%) is lower than that reported from studies in Russia (2004-08 – 25%)[28], France (2000-09 – 14%)[29], the UK (1990-2005 – 13%), Latin America (2002-12 - 20%)[30], and the USA (2008-2010 - 20%)[16], reflecting differences in background rates as well as in characteristics of the study populations.

We explored IDU history rather than current IDU given that IDU is a chronic and recurring condition. In our cohort, these women mainly had a history of injecting home-made opiates[31]. In the main adjusted models, IDU history was associated with an increased risk of PTD and of having a SGA infant, consistent with other studies of HIV-positive[15, 28, 29] and HIV-negative women, highlighting their need for a comprehensive package of care including opioid substitution therapy (as discussed previously in this cohort[31]). The 43% prevalence of smoking here is higher than that reported in a recent survey of reproductive-aged women in Ukraine (18% overall and 23% among 25-34 year-olds)[32], but consistent with higher rates among people living with HIV, including pregnant women[14, 33]. The smoking prevalence reported here is higher than in other studies of HIV-positive pregnant women (20% in Western European, 25% in Latin American, and 14-17% in US cohorts)[14, 16, 30, 33]. However, we lacked data on smoking during pregnancy, using self-reported smoking postnatally in a sub-cohort as a proxy for antenatal tobacco exposure, which may have over-estimated smoking in pregnancy. In sub-analysis incorporating smoking and maternal height, the 16% of women with heavy smoking had a significantly increased risk of PTD (AIRR 2·15), consistent with the literature on the effect of smoking in shortening gestation in general[11] and HIV-positive populations[33].

Maternal history of AIDS (WHO Stage 4) was associated with increased risk of PTD in adjusted analyses (AIRR 2·42), but was not associated with having an SGA infant. Other studies have also identified symptomatic HIV disease, AIDS or severe immunodeficiency to be associated with increased risk of PTD[15, 16, 29].

The associations between antenatal ART and adverse birth outcomes need careful interpretation given the changing clinical practices over the study period, during which the national PMTCT policy transitioned from use of ZDVm and/or single dose nevirapine to cART (predominantly boosted protease inhibitor-based)[7, 9]. Although we adjusted for WHO stage and calendar time, we had limited ability to adjust for confounding by indication for ART receipt in pregnancy in our main analyses as we were unable to adjust for CD4 cell count (not routinely available until after 2006) and as reasons for prescription of antenatal cART have changed over time[9]. cART (vs ZDVm) remained associated with PTD in a sub-analyses which included antenatal CD4 count, although some of the increased risk of PTD may have been due to residual confounding caused by more severe HIV disease in this group. The significant association between lack of antenatal ART and PTD (AIRR 2·94) may be partly explained by women delivering before having the opportunity to start ART, but also the likely correlation between non-receipt of ART and lack of or late presentation for antenatal care, a factor well known to be associated with PTD and SGA[34]. Our findings of an increased risk of PTD (AIRR 1·40)

and SGA (AIRR 1·33) associated with cART versus ZDVm here are consistent with other studies[14-17]. Preliminary data from the PROMISE trial indicated more severe pregnancy outcomes among infants exposed to tenofovir, emtricitabine and lopinavir/ritonavir than among those exposed to ZDV, lamivudine and lopinavir/ritonavir[35]. We detected no increased risk of PTD, SGA, or LBW among the small number of women receiving tenofovir-containing cART, but statistical power was limited. Evidence is growing of increased risks of PTD in women conceiving on cART and in those starting cART in pregnancy, with potentially different mechanisms[16, 29, 30]. We therefore plan further research focusing on timing and type of cART, particularly given the expanding use of cART in Ukraine in women before and during pregnancy[9].

The neonatal mortality rate was 4·62 per 1000 livebirths, comparable to the national estimate of 5/1000 in 2012. Comparison with other MTCT studies shows a similar rate in Latin America (4·0/1000 livebirths), another lower middle-income setting[30], and slightly lower rate in the UK (3·6/1000). PTD is the major cause of neonatal mortality worldwide and half the neonatal deaths here were in preterm infants.

Our study is limited by the potential for confounding and bias, including social desirability bias, e.g. regarding reporting of IDU and smoking. We lacked data on hypertension, sexually transmitted infections, prior PTD, second-hand smoke exposure, alcohol use, timing of antenatal care initiation and psycho-social stressors and were unable to include these known risk factors in our analyses. We also lacked data on a comprehensive range of socioeconomic indicators (e.g. employment and housing status) for inclusion in the SDI. Regarding generalizability of our findings, our study enrols approximately 30% of all HIV-positive women delivering nationally. Our inclusion of the SDI strengthens our study, given associations between social deprivation and adverse pregnancy outcomes.

In conclusion, in this large study of HIV-positive pregnant women, we have identified risk factors for PTD and SGA, some directly related to HIV infection, such as poor clinical status, and others shared by the general antenatal population, such as substance use and social deprivation. There are around 4000 deliveries to HIV-positive women in Ukraine annually[2]. Based on our findings, we can estimate that annually approximately 720 infants born to HIV-positive women will be preterm and/or SGA and 18 will die in the neonatal period; around 80-160 infants will be HIV-infected (one-fifth of whom will be preterm) based on current MTCT rates of 2-4%[2, 9], although this will decrease with increasing roll-out of antenatal cART for all HIV-positive pregnant women. There is focus on elimination of new infant HIV infections in Europe and globally[1]. Our findings indicate the importance of ensuring that on-going efforts to improve perinatal outcomes in Ukraine in general are extended to HIV-positive women. The association between antenatal cART and PTD in this population where cART has been available for PMTCT since 2007 requires further research and ongoing monitoring of pregnancy outcomes in the context of increasing use of cART.

Contributors
CTh and RM contributed to the design of the ECS and postnatal cohort. The Ukraine European Collaborative Study Group contributed to the acquisition of data. All authors contributed to the developing the concept of the article and interpreted the results. EB conducted the statistical analysis and MCB contributed to the statistical analysis. All authors contributed to drafting and revising the intellectual content of this manuscript and read and approved the final manuscript.

Declaration of interests
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T. Pilipenko (Perinatal Prevention of AIDS Initiative, Odessa, Ukraine); Dr S.Posokhova (Regional Hospital, Odessa, Ukraine); Dr T.Kaleeva, Dr Y. Barishnikova, Dr S. Servetsky, Dr R. Tereshenko (Odessa Regional Centre for HIV/AIDS, Ukraine); Dr S. Solokha, Dr M. P. Grazhdanov, Dr E. Kulakovskaya (Donetsk Regional Centre for HIV/AIDS, Ukraine); Dr I. Raus, Dr O. V. Yurchenko, Dr I. Adejnova (Kiev City Centre for HIV/AIDS, Ukraine); Dr Z. Ruban, Dr O.Govorun, Dr I. Kochergina, Dr L. Ostrovskaya (Mikolaiv Regional Centre for HIV/AIDS, Ukraine); Dr N. Primak; Dr. L. Kvasha, Dr.G. Kruglenko (Kriviy Rig City Center for HIV/AIDS, Ukraine); Dr A. Stelmah, Dr G. Kiseleva, Dr E. Dotsenko, Dr O. A. Zalata (Crimean Republic Centre for HIV/AIDS, Ukraine), Dr N.Bashkatova, Dr V. Gigil' (Mariupol AIDS Centre, Ukraine).

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Table 1. Maternal socio-demographic and clinical characteristics, (*n*=8884)

	n	**(%)**
Maternal age (years) , *n*=8863		
≤ 18	140	(1·6)
18 – 26	4587	(51·8)
27- 34	3475	(39·2)
≥35	661	(7·5)
WHO stage, n=7741		
Stage 1	6444	(83·2)
Stage 2	465	(6·0)
Stage 3	734	(9·5)
Stage 4	98	(1·3)
Parity, *n*=8488		
Nulliparous	4592	(54·1)
Primiparous	2812	(33·1)
Multiparous	1084	(12·8)
Maternal ethnicity, n=8824		
White	8694	(98·5)
Other	130	(1·5)
Marital status, n=8680		
Single	1388	(16·0)
Married	3790	(43·7)
Cohabiting	3502	(40·4)
History of IDU, *n*=8760		
Yes	1474	(16·8)
No	7286	(83·2)
Partner history of IDU, n=8623		
Yes	2526	(29·3)
No	6097	(70·7)
Timing of HIV diagnosis, n=8392		
Pre pregnancy	2951	(35·2)
1st trimester	1623	(19·3)
2nd trimester	2291	(27·3)
3rd trimester	1217	(14·5)
At delivery	310	(3·7)
Received ART during pregnancy, *n*=8856		
Yes	7348	(83·1)
No	1497	(16·9)
Type of antenatal ART, *n*=8842		
None	1497	(16·9)
ZDV monotherapy	4396	(49·7)
cART	2949	(33·4)
Timing of ART initiation, *n*=7282		
Pre-pregnancy	252	(3·5)
1st trimester	105	(1·4)
2nd trimester	3330	(45·7)
3rd trimester	3595	(49·4)
Social Deprivation Index, n=8884		
Least deprived	4141	(46·6)
More deprived	2833	(31·9)
Most deprived	1910	(21·5)

Delivery mode, *n*=8824		
Elective caesarean section	2619	(29·6)
Emergency caesarean section	344	(4·0)
Vaginal	5861	(66·4)
Smoking status[1], *n*=2078		
Non smoker	1175	(56·5)
Light to moderate smoker	569	(27·4)
Heavy smoker (≥20 cigarettes per day)	334	(16·1)

Abbreviations: IDU: Injecting drug use, ART: Antiretroviral therapy, ZDV: Zidovudine, cART: Combination antiretroviral therapy.

[1]Available in the postnatal sub-cohort only

Table 2 Risk factors for preterm delivery (*n*=7328)

	IRR	95% CI	AIRR†	95% CI	*p*-value
History of IDU					
Yes vs. no	**2·30ˆ**	**(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)	0·067
Most vs. least deprived	**1·51ˆ**	**(1·27, 1·81)**	**1·38**	**(1·11, 1·71)**	**0·004**
Parity					
1 vs. 0	**1·22ˆ**	**(1·04, 1,44)**	0·97	(0·82, 1·15)	0·737
≥2 vs. 0	**1·53ˆ**	**(1·24, 1·88)**	1·01	(0·81, 1·27)	0·905
WHO stage					
2 vs. 1	1·02	(0·73, 1·42)	0·85	(0·60, 1·21)	0·366
3 vs. 1	**1·66ˆ**	**(1·35, 2·04)**	**1·32**	**(1·06, 1·65)**	**0·015**
4 vs. 1	**3·69ˆ**	**(2·59, 5·26)**	**2·42**	**(1·71, 3·41)**	**<0·0001**
Antenatal ART					
None vs. ZDV monotherapy	**3·45ˆ**	**(2·88, 4·14)**	**2·94**	**(2·43, 3·57)**	**<0·0001**
cART vs. ZDV monotherapy	**1·75ˆ**	**(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)					
≤18 vs. 18-26	0·90	(0·43, 1·86)	0·84	(0·42, 1·71)	0·650
27-34 vs. 18-26	**1·50ˆ**	**(1·28, 1·76)**	**1·28**	**(1·08, 1·51)**	**0·003**
≥35 vs. 18-26	**1·97ˆ**	**(1·55, 2·51)**	**1·55**	**(1·20, 1·99)**	**0·001**

Abbreviations: IRR: Incidence risk ratio, AIRR: Adjusted incidence risk ratio, IDU: Injecting drug use, ART: Antiretroviral therapy, ZDV: Zidovudine, cART: Combination antiretroviral therapy.

ˆSignificant in the univariable analysis

†Adjusted for study centre, antenatal ART, IDU history, SDI, parity, WHO stage, maternal age and calendar year

Table 3 Risk factors for delivery of a SGA infant (*n*=7581)

	IRR	95% CI	AIRR[†]	95% CI	*p*-value
History of IDU					
Yes vs. No	**1·57**[ˆ]	**(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)	0·152
Most vs. least deprived	**1·39**[ˆ]	**(1·17, 1·63)**	**1·32**	**(1·09, 1·61)**	**0·006**
WHO stage					
2 vs. 1	1·02	(0·76, 1·36)	0·96	(0·71, 1·31)	0·818
3 vs. 1	**1·28**[ˆ]	**(1·04, 1·58)**	1·12	(0·89, 1·40)	0·335
4 vs. 1	**1·73**[ˆ]	**(1·08, 2·76)**	1·46	(0·90, 2·37)	0·126
Antenatal ART					
None vs. ZDVm	**1·87**[ˆ]	**(1·56, 2·23)**	**1·60**	**(1·32, 1·94)**	**<0·0001**
cART vs. ZDVm	**1·43**[ˆ]	**(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)	0·523
Maternal age (years)					
≤18 vs. 18-26	0·74	(0·38, 1·46)	0·71	(0·36, 1·39)	0·312
27-34 vs. 18-26	1·12	(0·98, 1·30)	1·03	(0·89, 1·19)	0·730
≥35 vs. 18-26	**1·35**[ˆ]	**(1·07, 1·72)**	1·18	(0·93, 1·50)	0·178

Abbreviations: IRR: Incidence risk ratio, AIRR: Adjusted incidence risk ratio, IDU: Injecting drug use, ART: Antiretroviral therapy, ZDV: Zidovudine, cART: Combination antiretroviral therapy.

[ˆ]Significant in the univariable analysis

[†]Adjusted for study centre

Research in context

Evidence before this study

This is the first study of adverse birth outcomes among HIV-positive pregnant women in Ukraine. Published data on preterm delivery (PTD) rates in Eastern Europe are scarce but individual studies have reported rates from 5%-12% among the general population and 25% among HIV-positive women in Russia. Concerns regarding PTD among HIV-positive women, first raised more than 20 years ago, were initially focused on the impact of HIV and immunosuppression and then on combined antiretroviral therapy (cART) regimens, as well as traditional risk factors for PTD. Pregnancy outcomes among HIV-positive women need to be understood in the context of substantial variation between populations, to inform country-specific prevention of mother-to-child transmission (PMTCT) and maternal and child health programmes.

Added value of this study

In this study of nearly 9000 HIV-positive women in Ukraine delivering liveborn infants from 2000 to 2012, 9% of deliveries were preterm with cumulative prevalence of PTD and SGA of 18%. Our results indicate that around 720 preterm and/or SGA infants were born to HIV-positive women annually at the end of this time period, with some risk factors directly related to HIV infection such as poor clinical status and cART use and others shared by the general antenatal population including substance use and social deprivation. The increase in PTD over the 13 years of this study, independently of cART scale-up since 2007, highlights the importance of further work to monitor outcomes and delineate contemporary risk factors, as antenatal cART coverage increases in this lower middle-income setting.

Implications of all the available evidence

This study spans pre-ART, zidovudine monotherapy and cART eras for HIV-positive pregnant women in Ukraine, addressing an important evidence gap on the evolution of and risk factors for adverse pregnancy outcomes in this population. We plan further research to assess the impact of antenatal cART as data accumulates on its use in Ukraine.

EuroCoord Appendix

EuroCoord Executive Board: Fiona Burns, University College London, UK; Geneviève Chêne, University of Bordeaux, France; Dominique Costagliola (Scientific Coordinator), Institut National de la Santé et de la Recherche Médicale, France; Carlo Giaquinto, Fondazione PENTA, Italy; Jesper Grarup, Region Hovedstaden, Denmark; Ole Kirk, Region Hovedstaden, Denmark; Laurence Meyer, Institut National de la Santé et de la Recherche Médicale, France; Heather Bailey, University College London, UK; Alain Volny Anne, European AIDS Treatment Group, France; Alex Panteleev, St. Petersburg City AIDS Centre, Russian Federation; Andrew Phillips, University College London, UK, Kholoud Porter, University College London, UK; Claire Thorne, University College London, UK.

EuroCoord Council of Partners: Jean-Pierre Aboulker, Institut National de la Santé et de la Recherche Médicale, France; Jan Albert, Karolinska Institute, Sweden; Silvia Asandi , Romanian Angel Appeal Foundation, Romania; Geneviève Chêne, University of Bordeaux, France; Dominique Costagliola (chair), INSERM, France; Antonella d'Arminio Monforte, ICoNA Foundation, Italy; Stéphane De Wit, St. Pierre University Hospital, Belgium; Peter Reiss, Stichting HIV Monitoring, Netherlands; Julia Del Amo, Instituto de Salud Carlos III, Spain; José Gatell, Fundació Privada Clínic per a la Recerca Bíomèdica, Spain; Carlo Giaquinto, Fondazione PENTA, Italy; Osamah Hamouda, Robert Koch Institut, Germany; Igor Karpov, University of Minsk, Belarus; Bruno Ledergerber, University of Zurich, Switzerland; Jens Lundgren, Region Hovedstaden, Denmark; Ruslan Malyuta, Perinatal Prevention of AIDS Initiative, Ukraine; Claus Møller, Cadpeople A/S, Denmark; Kholoud Porter, University College London, United Kingdom; Maria Prins, Academic Medical Centre, Netherlands; Aza Rakhmanova, St. Petersburg City AIDS Centre, Russian Federation; Jürgen Rockstroh, University of Bonn, Germany; Magda Rosinska, National Institute of Public Health, National Institute of Hygiene, Poland; Manjinder Sandhu, Genome Research Limited; Claire Thorne, University College London, UK; Giota Touloumi, National and Kapodistrian University of Athens, Greece; Alain Volny Anne, European AIDS Treatment Group, France.

EuroCoord External Advisory Board: David Cooper, University of New South Wales, Australia; Nikos Dedes, Positive Voice, Greece; Kevin Fenton, Public Health England, USA; David Pizzuti, Gilead Sciences, USA; Marco Vitoria, World Health Organisation, Switzerland.

EuroCoord Secretariat: Silvia Faggion, Fondazione PENTA, Italy; Lorraine Fradette, University College London, UK; Richard Frost, University College London, UK; Andrea Cartier, University College London, UK; Dorthe Raben, Region Hovedstaden, Denmark; Christine Schwimmer, University of Bordeaux, France; Martin Scott, UCL European Research & Innovation Office, UK