Nucleoside reverse transcriptase inhibitor backbones and pregnancy outcomes

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The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Study Group*

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Abstract

Objectives: to investigate whether specific nucleoside reverse transcriptase inhibitor (NRTI) backbones are associated with risk of adverse pregnancy outcomes among pregnant women starting antiretroviral therapy (ART)

Design: Seven observational studies across eight European countries of pregnancies in HIV-positive women

Methods: Individual-level data were pooled on singleton pregnancies conceived off-ART in which a single combination ART regimen was initiated ≥2 weeks before delivery, and ending in a live birth in 2008-2014. Preterm delivery (PTD) was defined as <37 gestational weeks and small-for-gestational-age (SGA) as <10th percentile according to INTERGROWTH standards. Poisson regression models were fitted to investigate associations between NRTI backbones and PTD/SGA.

Results: Of 7193 pregnancies, 45% (3207) were in UK/Ireland, 44% (3134) in Ukraine. 10% (722/7193) of deliveries were preterm and 11.1% (785/7089) of newborns SGA. The most common NRTI backbones were ZDV-3TC (71%), TDF-XTC (16%) and ABC-3TC (10%) with TDF-containing backbone use increasing over time. Overall, 77% of regimens contained LPV/r. There was no association between NRTI backbone and PTD in main adjusted analyses (adjusted prevalence ratios (aPR) 0.97 [95%CI 0.73-1.28] for ABC-3TC and aPR 1.06 [0.83-1.35] for TDF-XTC, both vs ZDV-3TC) or in 4720 pregnancies on LPV/r (aPR 1.03 [0.74-1.43] for ABC-3TC and aPR 1.16 [0.85-1.57] for TDF-XTC, both vs ZDV-3TC). Infants exposed to ABC-3TC or TDF-XTC in-utero were less likely to be SGA than those exposed to ZDV-3TC (aPR 0.72 [0.53-0.97] and aPR 0.70 [0.53-0.93] respectively).

Conclusions: Results support the safety of TDF-XTC backbones initiated in pregnancy with respect to gestation length and birthweight.

Key words: HIV, pregnancy, preterm delivery, small-for-gestational age, antiretroviral therapy, NRTI backbones, Europe

Introduction

Around 76% of the 1.4 million pregnant women living with HIV in 2016 worldwide received antiretroviral therapy (ART) during their pregnancy to prevent mother-to-child transmission (MTCT) [1]. Most received a three-drug regimen, as recommended by WHO for all HIV-positive pregnant women since 2013, with tenofovir (TDF) plus emtricitabine (FTC) and efavirenz (EFV) as first-line [2]. Widespread antenatal and postnatal ART along with other interventions has reduced HIV MTCT rates to "elimination" levels in some high prevalence settings [1], and to around <1% in Western Europe [3-6] and 1-4% in Eastern Europe [7][8]). However combination ART (cART) has been associated with increased risk of some adverse pregnancy outcomes including preterm delivery (PTD) and small-for-gestational age (SGA), as compared with mono/dual therapy [9-12].

Results of studies vary with respect to the safest ART regimens/component drugs in pregnancy. Boosted protease inhibitors (PIs) and particularly ritonavir-boosted lopinavir (LPV/r) have been associated with increased risk of PTD [13] while results from the PROMISE trial led to a focus on the safety of TDF. In this trial, which took place in India, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe, LPV/r given with a TDF-FTC backbone was associated with higher risk of delivery <34 weeks and neonatal death by 14 days than when given with a zidovudine (ZDV) - lamivudine (3TC) backbone among women starting ART in pregnancy [11]. In contrast, population-based data from Botswana (a context with high prevalence of adverse pregnancy outcomes overall) has been reassuring with regard to the safety of TDF-containing regimens, with no difference in PTD rates among women starting TDF-FTC-EFV vs other ART regimen in pregnancy [14] although a lower risk of SGA among pregnancies exposed to TDF-FTC-EFV vs TDF-FTC-LPV/r or TDF-FTC-NVP from conception [14, 15]. Similarly, US data do not indicate an increased risk of adverse pregnancy outcomes with

TDF-FTC-LPV/r compared with ZDV-3TC-LPV/r [16], while a recent meta-analysis found no increased risk of a range of adverse pregnancy, maternal and infant outcomes among women on TDF-containing regimens and a lower risk of preterm delivery and stillbirth [17].

Aetiologies of adverse pregnancy outcomes are complex and overlapping, with severity of HIV infection and other factors such as malnutrition, maternal age, injecting drug use (IDU) and co-infections implicated in increasing risk as well as specific ART regimens. This may explain the conflicting findings between studies conducted in different populations, alongside other factors such as timing of ART initiation. The majority of HIV-positive pregnant women in Europe are now on ART at conception [3, 18], and this proportion is increasing in high prevalence settings with adoption of treat all approaches. However, almost half of people living with HIV worldwide in 2016 were not yet on treatment [19]; data regarding the safest ART regimens for those newly initiating treatment during pregnancy therefore remain important.

Our aim was to investigate whether specific NRTI backbones were associated with risk of adverse pregnancy outcomes among women starting ART during pregnancy, in resource-rich and middle income settings in Western and Eastern Europe.

Methods

We conducted a pooled analysis of pregnancies in HIV-positive women from observational studies participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC).

Study population

Singleton pregnancies ending in a live birth in 2008 to 2014, conceived off treatment and in which a single cART regimen was initiated were eligible for inclusion in this study. cART was defined as 3 or 4 antiretroviral drugs, including ≥2 NRTIs, started within a 7 day period. We took this approach to minimise treatment bias by timing of ART initiation and to explore the safety of ART regimens started during pregnancy, given differences in outcomes reported by timing of initiation [20]. The combination of TDF with either 3TC or FTC is referred to as TDF-XTC throughout.

Exclusion criteria were: reported duration of ART <2 weeks (*n*=148); enrolment in a country with <10 eligible pregnancies; (*n*=12) ART switches or substitutions (defined as ≥5 antiretrovirals (ARVs) received in pregnancy, or 4 ARVs if difference of >7 days in start dates) (*n*=495); missing data on gestation at delivery (*n*=64).

Seven studies across eight countries in Western and Eastern Europe had pregnancies meeting the inclusion criteria. Anonymous individual-level data were pooled using a standard operating procedure based on HIV Cohorts Data Exchange Protocol (hicdep.org) data specification. The studies participating in the data merger were each responsible for ensuring that appropriate ethics approvals were in place, and for compliance with data protection requirements. Variables included sociodemographic, clinical and treatment factors, and pregnancy and neonatal outcomes.

Definitions

PTD was defined as delivery at <37 completed weeks gestation and very PTD at <34 weeks. SGA was defined as <10th percentile according to INTERGROWTH standards [21, 22]. Gestational age was predominantly determined by ultrasound (coverage of >95% in Ukraine [23] and in Western European countries). Neonatal death was defined as within the first 28 days.

Statistical analysis

Univariable comparisons of categorical variables were assessed using Chi-squared or Fisher's exact tests. The Wilcoxon-Mann-Whitney rank sum test was used to compare continuous variables. Adjusted prevalence ratios (aPR) were estimated by fitting Poisson regression models with robust estimates to investigate associations between NRTI backbone and 1) PTD, 2) very PTD and 3) SGA, adjusted *a priori* for potential confounders (for PTD models: calendar year and country of delivery, parity, maternal IDU history, CD4 count, maternal age, third agent in the ART regimen; for SGA model: all variables included in the PTD models plus infant sex and ART duration).

Outcomes were also assessed in sub-analyses restricted to pregnancies initiated on a LPV/r-containing regimen (which increases TDF blood levels when co-administered). These models were conducted on a complete case basis and adjusted for the variables included in the main model. Statistical analyses were carried out using STATA v13.1 software (Stata Corp, College Station, Texas, USA).

Results

Maternal characteristics and pregnancy outcomes

Of 7193 pregnancies included in these analyses, 45% (3207) were in the UK and Ireland, 44% (3134) in Ukraine and 7% (469) in Russia, with smaller numbers in Belgium, Romania, Spain and Switzerland (Table 1). Overall, 52% of pregnancies were in women newly diagnosed with HIV during that pregnancy, 37% in Black women (ranging from 77% (2469/3199) in the UK/Ireland to none in Russia and 0.6% (2/3116) in Ukraine) and 7% were in women with a history of IDU (ranging from 11% in Ukraine (355/3125) and 9% in Russia (41/454) to 2% in UK and Ireland (49/2948) and none in Belgium and Switzerland). Median first CD4 count in pregnancy was 396 cells/mm^3 [interquartile range (IQR) 260, 559] with no difference by timing of HIV diagnosis (before/during pregnancy, p=0.186). ART was started at median 22.9 gestation weeks [IQR 18.9, 25.7] and received for median 15.7 weeks by delivery [IQR 12.3, 19.6].

Overall 10% (n=722) of deliveries were preterm and 3.4% (n=246) were very preterm; 11.1% (785/7089) of infants were SGA. There were 92 (1.3%) infants who were both preterm and SGA, representing 11.7% (92/785) of the SGA group and 13% (92/707) of the PTD group (birthweight missing for 15 preterm infants). Rates of PTD and SGA differed by country (supplementary Table A). The rate of low birthweight (<2500g) among term infants was 6.7% (431/6471). The unadjusted MTCT rate was 1.11% (95% CI 0.85-1.42) (HIV status known for 77% (5511/7193) infants). There were 21 neonatal deaths among 6689 infants with data available, giving a neonatal mortality rate (NMR) of 3.1 per 1000 live births. Of the 21 neonates who died, 13 were preterm (10/13 <34 weeks) and 3 were SGA (2/3 preterm). The NMR among very preterm, preterm and SGA infants was 40.7, 18.0 and 3.8 per 1000 live births respectively.

Trends in NRTI backbones and ART regimens over time

In 71% (5122/7193) of pregnancies the ART regimen included ZDV-3TC, in 16% (1122/7193) TDF-XTC and in 10% (711/7193) 3TC plus abacavir (ABC). Use of ZDV-3TC declined over time, with increasing use of other regimens, particularly TDF-containing backbones (Figure 1). The most commonly used third agent was ritonavir-boosted LPV/r, used in 77% (5558/7193) of regimens overall, of which 81% (4527/5558) contained a ZDV-3TC backbone (Figure 2). Of regimens based on other PIs, 30% (283/934) contained a ZDV-3TC backbone and 49% (456/934) a TDF-XTC backbone. NNRTIs were used in 7% (517/7193) of pregnancies overall (most commonly nevirapine (NVP), which accounted for 416 of 517 NNRTI-based regimens). Use of ARVs varied substantially by country with LPV/r-based regimens most commonly used in Ukraine and Russia, see supplementary table A.

NRTI backbone and PTD risk

Overall, PTD rates for the four most commonly used regimens were: 10.2% (461/4527) for LPV/r-ZDV-3TC; 10.0% (46/461) for LPV/r-ABC-3TC; 11.6% (53/457) for LPV/r-TDF-XTC; 11.2% (51/456) for other PI-TDF-XTC. There was no difference in PTD rate according to inclusion in the complete case analysis (PTD rate was 10.2% (626/6123) in included vs. 9.0% (96/1070) in excluded pregnancies, p=0.209). However, there was a slight difference in NRTI backbones received: ZDV-3TC was received in 71.8% of included pregnancies vs 67.7% excluded; ABC-3TC in 9.5% included pregnancies vs 12.1% excluded; TDF-XTC in 15.4% of included vs 16.8% excluded; other NRTI backbone in 3% in both groups, p=0.023). In the main model adjusting for third agent and other factors (Table 2, N=6123), there was no association between NRTI backbone and PTD. Pregnancies in women with a CD4 count <200 vs. ≥350, aged 30-39 vs 21-29 years, and with an IDU history were more likely to be delivered preterm, as were pregnancies in which a LPV/r-based ART regimen was received.

In the sub-analysis among 4720 pregnancies on LPV/r and adjusted as for the main model, NRTI backbone remained unassociated with PTD risk (aPR 1.03 95% CI 0.74-1.43, *p*=0.873 for ABC-3TC, aPR 1.16 95% CI 0.85-1.57, *p*=0.351 for TDF-XTC and aPR 0.59 95% CI 0.28-1.24 *p*=0.166 for other NRTI backbone, all vs. ZDV-3TC).

Very PTD rates <34 weeks were 3.4% (173/5122) for ZDV-3TC, 2.8% (20/711) for ABC-3TC, 3.7% (42/1122) for TDF-XTC and 4.6% (11/238) for other NRTI backbones. There was no indication of an association between NRTI backbone in adjusted analyses (aPR 0.93 95% CI 0.54-1.60, *p*=0.790 for ABC-3TC, aPR 1.27 95% CI 0.84-1.91, *p*=0.259 for TDF-XTC and aPR 1.22 95% CI 0.61-2.42 *p*=0.569 for other NRTI backbone, all vs. ZDV-3TC), and no increased risk of very PTD with LPV/r vs. other PIs (aPR 1.17 95% CI 0.75-1.82 *p*=0.498).

NRTI backbone and SGA

The SGA rate was the same among the 5780 pregnancies included in the complete case analysis and those excluded (both 20.9%, 1209/5780 and 273/1309). However, the distribution of NRTI backbones was significantly different between the two groups (*p*<0.001): comparing included with excluded pregnancies, ZDV-3TC was received in a greater proportion of the former (72.2% vs 67.0%) and ABC-3TC and TDF-XTC in smaller proportions (9.7% vs 10.5% and 14.8% vs 19.0% respectively), with no difference in other NRTI backbones (3.3% vs 3.4%). Infants exposed in utero to ABC-3TC or TDF-XTC were less likely to be SGA than those exposed to ZDV-3TC in both unadjusted and adjusted analyses (Table 3, N=5780). Although LPV/r was associated with SGA in unadjusted analyses, there was no difference by third agent after adjusting for NRTI backbone and the other factors in the multivariable model. Increased risk of SGA was also observed in infants born to nulliparous women and those whose mothers had a history of IDU.

In the model restricted to 4482 pregnancies with LPV/r, NRTI backbone was no longer associated with risk of SGA (aPR 0.73 95% CI 0.52-1.03, *p*=0.076 for ABC+3TC, aPR 0.75 95% CI 0.53-1.06, *p*=0.100 for TDF-XTC and aPR 1.08 95% CI 0.65-1.79, *p*=0.763 for other NRTI backbone, all vs ZDV-3TC).

Discussion

In this pooled analyses of over 5700 pregnancies in HIV-positive women delivering in Europe in 2008-2014 who started ART during pregnancy, we found no increased PTD risk among those initiating a TDF-containing regimen and a decreased risk of SGA in newborns exposed in-utero to TDF-XTC or ABC-3TC compared with those exposed to ZDV-3TC. The use of ART regimens changed substantially over time, with TDF-containing backbones accounting for an increasing proportion of regimens overall in more recent years, used mostly in combination with PIs other than LPV/r and accounting for over 20% of regimens in 2014.

Among pregnancies on LPV/r-based regimens, those with a TDF-XTC backbone had a slightly higher unadjusted PTD rate than other regimens (11.6% vs around 10%); however, the former were initiated earlier in pregnancy, increasing the opportunity for PTD after ART initiation, and included a greater proportion of Black African women, a factor independently associated with shorter gestation [24]. In analyses adjusting for country, year and other factors, we found no association between NRTI backbone and PTD or very PTD. This is in contrast with the PROMISE study [11] but in line with other studies that have found no difference or a reduced risk of PTD with TDF-containing regimens [14, 25, 26] and a recent meta-analysis which found TDF to be associated with a 10% reduction in PTD overall (RR 0.90, 95%CI 0.81; 0.99 vs non-TDF containing ART regimens) [17]. In a sub-analysis of pregnancies with LPV/r, there remained no association between NRTI backbone and PTD. Our findings add to the evidence base supporting the safety of TDF-XTC in pregnancy with respect to gestation length.

LPV/r was associated with an increased risk of PTD overall (aPR 1.32), an association previously reported in the UK and Ireland in women starting LPV/r pre-conception but not antenatally [27] and in an 2000-2012 Ukraine analyses in which only 4% of pregnancies were conceived on ART, with cART (89% LPV/r-based) associated with a 40% increased risk of PTD compared with zidovudine monotherapy [9]. However, in a study in Uganda there was no difference in PTD risk between women randomised to LPV/r-ZDV-3TC and EFV-ZDV-3TC at 12-28 weeks (16% and 15% delivered preterm respectively) [28]. Although its use is declining in Western Europe, LPV/r is still used widely in pregnancy in Ukraine and Russia where other risk factors for PTD (e.g. IDU history and smoking) are also more prevalent in HIV-positive women [9], and is a second-line option in high prevalence settings [29].

Of the 1099 singleton infants in our study exposed to TDF-XTC in utero, 8.6% were SGA compared with 11.7% exposed to ZDV-3TC, corresponding to a 35% reduced risk of SGA in adjusted analyses. The number of pregnancies in which ABC-3TC was initiated was smaller, but a reduced risk of SGA was also detected in these pregnancies vs those with ZDV-3TC in main (although not sensitivity) analyses. A meta-analysis of five previous studies found no association between TDF-containing ART and low birthweight (RR 0.91, 95% 0.80; 1.04) or weight-for-age Z scores at birth (mean difference -0.00 95% CI -0.11; 0.11) [17]. However, a reduced risk of SGA with TDF-XTC backbone has previously been reported in national surveillance data from Botswana, in which 1461 infants exposed to TDF-FTC-EFV in utero (started antenatally) had a 50% reduced risk of SGA compared with infants exposed to other three-drug ART regimens, predominantly ZDV-3TC-NVP [14]. In a further analysis from Botswana, where ART was initiated before conception, SGA risk was also lower with TDF-FTC-EFV than all other three-drug ART regimens, although the reduced risk was not specific to TDF-XTC regimens per se (adjusted risk ratio of 1.62 (1.29-2.03) for TDF-FTC-LPV/r vs TDF-FTC-EFV)

[15]. In our study, LPV/r was associated with SGA in unadjusted analyses but not after adjusting for NRTI backbone and other factors.

Although women starting ART in pregnancy have been found in other studies to have lower PTD risk than those conceiving on ART [20], confounding by ART indication complicates these comparisons with important differences in risk by immunological status [27]. Lifelong continuation of ART initiated in pregnancy (and therefore taken from conception in subsequent pregnancies) means that the broader safety profile of ART regimens need to be considered for women starting ART during pregnancy, including where – as with LPV/r – there is evidence of differential risk by timing of ART initiation [27]. An improved understanding of mechanisms by which ART may influence the risk of adverse pregnancy outcomes (which may include derangement of progesterone and/or estradiol levels [30, 31]) is needed to inform treatment guidelines for women starting ART within and outside of the context of pregnancy.

In the present study, PTD risk was higher in the 14% of pregnancies with a first antenatal CD4 count <200 cells/mm^3; approximately half of these women were already diagnosed before conception. This reflects CD4 eligibility cut-offs for treatment in earlier years (e.g. <350 cells/mm^3 in UK 2008 guidelines [32] and in Ukraine up to 2015 [8]), low ART coverage in Ukraine and possible disengagement from HIV care of previously diagnosed women [33], and highlights the potential impact of a treat all approach on improving pregnancy outcomes.

IDU history is an established risk factor for adverse pregnancy outcomes [34] and was associated with a two-fold increased risk of PTD and 50% increased risk of SGA in this study. One in ten women from Eastern European cohorts had an IDU history, versus less than 2% in the UK/Ireland, reflecting the different epidemiology of HIV in Western and Eastern Europe [9, 35, 36]. Given barriers to testing and treatment services experienced by some women who

inject drugs [37], they may continue to be an important group among those initiating ART during pregnancy in future years.

Limitations

Analyses exploring the role of timing of ART initiation or duration of ART in relation to PTD risk are prone to selection bias because pregnancies delivered preterm have by definition less opportunity to start ART in the later weeks [38]. For this reason, we did not explore ART duration in PTD analyses.

Our exclusion of 148 pregnancies with <2 weeks of ART may have resulted in under-estimation of the overall PTD rate, while exclusion of 495 pregnancies with ART switch may have resulted in selection bias if the reason for switch was related to the ART regimen received as well as risk of PTD or SGA (reason for switch was not consistently available). In addition, we did not have information available on some important confounders, for example smoking, BMI, history of adverse pregnancy outcomes, concurrent infections in pregnancy, ART adherence; the uneven distribution of these factors between countries as well as changes in national and international ART guidelines may have resulted in residual and uncontrolled confounding. Our study dataset was dominated by the UK/Ireland and Ukraine, and overall findings may not be generalizable to countries with smaller numbers of included pregnancies. Although the third agents used became more diverse over time, LPV/r-based regimens predominated overall and the proportion of pregnancies with NNRTI-based (and particularly EFV-based) regimens was limited.

Conclusions

In this pooled analysis of pregnancies in HIV-positive women in Europe from 2008-2014, there was no evidence of an association between NRTI backbone and PTD. Infants exposed to ABC-

3TC or TDF-XTC were in utero were significantly less likely to be born SGA than those exposed to ZDV-3TC. Taken together, results support the safety of TDF-XTC backbones initiated in pregnancy, with respect to gestation length and birthweight, as recommended first-line in WHO guidelines.

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Table 1: Maternal and pregnancy characteristics by NRTI backbone

	ZDV - 3TC	3TC - ABC	TDF – XTC	Other NRTI backbone	Total
	n=5122	*n*=711	*n*=1122	*n*=238	*n*=7193
	n (%) or median [IQR]				
Country (*n*=7193)					
UK and Ireland	2009 (39)	297 (42)	793 (71)	108 (45)	3207 (45)
Belgium	63 (1)	4 (1)	24 (2)	1 (0)	92 (1)
Romania	21 (0)	5 (1)	0 (0)	3 (1)	29 (0)
Russia	402 (8)	4 (1)	0 (0)	63 (26)	469 (7)
Spain	104 (2)	4 (1)	57 (5)	10 (4)	175 (2)
Switzerland	62 (1)	8 (1)	16 (1)	1 (0)	87 (1)
Ukraine	2461 (48)	389 (55)	232 (21)	52 (22)	3134 (44)
Year of delivery					
2008-2009	1939 (38)	167 (23)	146 (13)	48 (20)	2300 (32)
2010-2012	2369 (46)	309 (43)	562 (50)	95 (40)	3335 (46)
2013-2014	814 (16)	235 (33)	414 (37)	95 (40)	1558 (22)
Timing of HIV diagnosis (*n*=6994)					
Before pregnancy	2266 (45)	354 (50)	618 (58)	139 (60)	3377 (48)
During pregnancy	2722 (55)	349 (50)	453 (42)	93 (40)	3617 (52)
Maternal age (years) (*n*=7172)	28 [25, 32]	29 [25, 33]	30 [26, 35]	29 [26, 33]	29 [25, 33]
Parity (*n*=7174)					

0	2361 (46)	308 (43)	443 (40)	96 (41)	3208 (45)
1	1800 (35)	237 (33)	349 (31)	90 (38)	2476 (35)
≥2	949 (19)	166 (23)	324 (29)	51 (22)	1490 (21)
Ethnicity (*n*=7108)					
White	3258 (64)	418 (59)	405 (37)	136 (58)	4217 (59)
Black	1655 (33)	266 (37)	643 (59)	91 (39)	2655 (37)
Other	153 (3)	27 (4)	48 (4)	8 (3)	236 (3)
History of injecting drug use (*n*=6845)					
No	4538 (92)	652 (95)	980 (96)	216 (95)	6386 (93)
Yes	372 (8)	36 (5)	40 (4)	11 (5)	459 (7)
CD4 count (cells/mm^3) (*n*=6440)†					
<200	585 (13)	105 (17)	199 (19)	36 (17)	925 (14)
200-349	1174 (26)	196 (33)	278 (27)	40 (19)	1688 (26)
≥350	2831 (62)	302 (50)	560 (54)	134 (64)	3827 (59)
Third agent					
LPV/r	4527 (88)	461 (65)	457 (41)	113 (47)	5558 (77)
Other PI	283 (6)	177 (25)	456 (41)	18 (8)	934 (13)
NNRTI	294 (6)	65 (9)	146 (13)	12 (5)	517 (7)
PI-NNRTI /Fusion /Integrase /only NRTIs	18 (0.4)	8 (1)	63 (6)	95 (40)	184 (3)

Timing of ART initiation	23.1	23.4	20.4	23	22.9
(weeks gestation)	[19.6, 25.7]	[19.1, 26.4]	[16.1, 24.4]	[18.6, 28]	[18.9, 25.7]
(*n*=6858)					

†First antenatal CD4 count

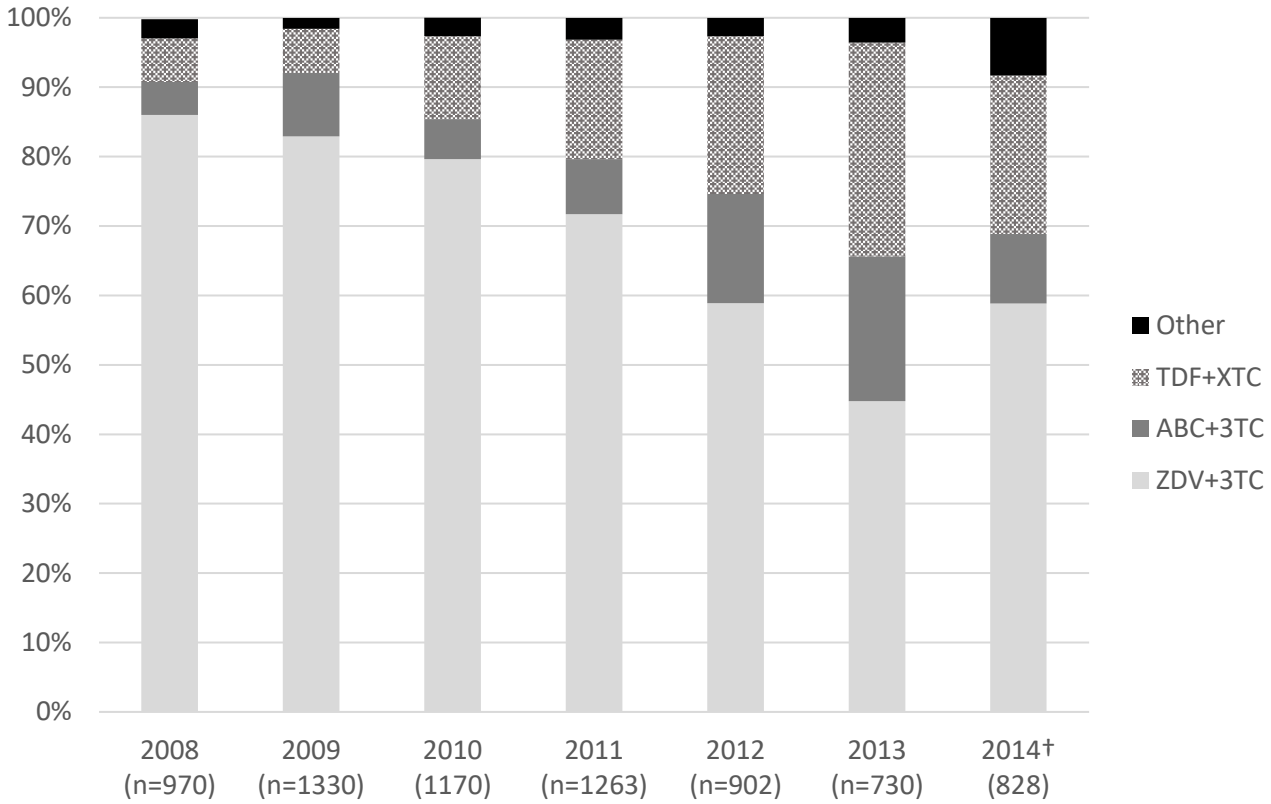

Figure 1: Change in NRTI backbone use over calendar time

†Most (430/469) pregnancies in the Russian cohort were in 2014; use of ZDV-3TC predominated in this cohort. In the other 6 countries, ZDV-3TC use declined to 30% (118/398) in 2014 and TDF-XTC use increased to 47% (189/398) of all regimens.

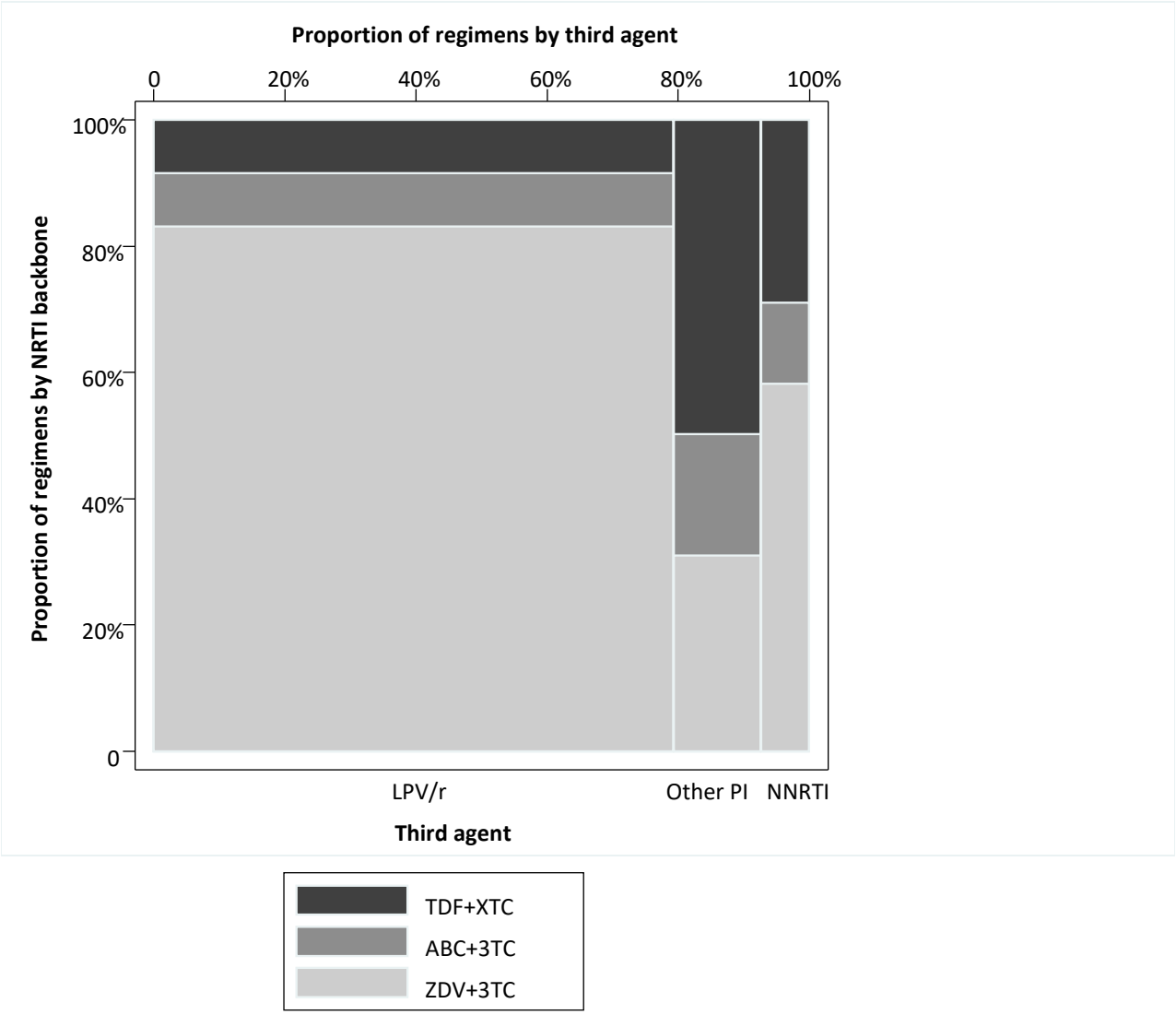

Figure 2: NRTI backbone and third agent combinations

Mosaic plot showing combinations of third agent and NRTI backbone in 6866 pregnancies. The 327 pregnancies in which the NRTI backbone was one other than the three shown, the regimen consisted only of NRTIs and/or the third agent was PI+NNRTI /Fusion /Integrase are not shown on this plot.

Table 2: Factors associated with preterm delivery <37 weeks

	Proportion of deliveries <37 weeks	Crude prevalence ratio (95% CI) N=6123	*p* value	Adjusted prevalence ratio (95% CI)† N=6123	*p* value
NRTI backbone					
ZDV+3TC	10.1% (516/5122)	1.00		1.00	
ABC+3TC	9.3% (66/711)	0.90 (0.69, 1.18)	0.436	0.97 (0.73, 1.28)	0.822
TDF+XTC	10.5% (118/1122)	1.03 (0.84, 1.26)	0.789	1.06 (0.83, 1.35)	0.658
Other	9.2% (22/238)	0.87 (0.55, 1.36)	0.535	0.78 (0.48, 1.27)	0.326
CD4 count (cells/mm^3)					
≥350	9.4% (358/3827)	1.00		1.00	
200-349	10.5% (177/1688)	1.11 (0.93, 1.32)	0.233	1.14 (0.96, 1.36)	0.131
<200	11.9% (110/925)	1.30 (1.06, 1.59)	0.012	1.32 (1.07, 1.64)	0.010
Maternal age (years)					
21-29	9.2% (322/3506)	1.00		1.00	

≤20	9.3% (38/411)	1.13 (0.81, 1.57)	0.484	1.13 (0.81, 1.59)	0.466
30-39	11.3% (344/3051)	1.29 (1.11, 1.51)	0.001	1.21 (1.03, 1.43)	0.022
≥40	7.8% (16/204)	1.01 (0.63, 1.64)	0.960	0.91 (0.55, 1.48)	0.697
Calendar year (per increasing year)		1.01 (0.97, 1.05)	0.647	1.01 (0.96, 1.06)	0.626
Parity					
≥2	11.1% (166/1490)	1.00		1.00	
1	9.8% (243/2476)	0.86 (0.71, 1.06)	0.152	0.89 (0.72, 1.10)	0.277
0	9.7% (312/3208)	0.90 (0.74, 1.09)	0.264	0.95 (0.78, 1.17)	0.655
IDU history					
No	9.7% (620/6386)	1.00		1.00	
Yes	17.7% (81/459)	1.94 (1.55, 2.42)	<0.001	2.07 (1.64, 2.61)	<0.001
Third agent					
Other PI	8.9% (83/934)	1.00		1.00	
LPV/r	10.3% (570/5558)	1.12 (0.89, 1.42)	0.322	1.32 (1.01, 1.72)	0.042
NNRTI	9.9% (51/517)	1.13 (0.79, 1.60)	0.510	1.17 (0.81, 1.68)	0.410

PI+NNRTI /Fusion /Integrase /only NRTIs	9.8% (18/184)	1.10 (0.66, 1.83)	0.725	1.25 (0.73, 2.15)	0.413

† Adjusted also for country of delivery

Table 3: Factors associated with SGA

	Proportion of infants SGA	Crude prevalence ratio (95% CI) N=5780	*p* value	Adjusted prevalence ratio (95% CI)† N=5780	*p* value
NRTI backbone					
ZDV+3TC	11.7% (591/5045)	1.00		1.00	
ABC+3TC	9.9% (70/709)	0.69 (0.52, 0.91)	0.010	0.72 (0.53, 0.97)	0.029
TDF+XTC	8.6% (94/1099)	0.65 (0.51, 0.82)	<0.001	0.70 (0.53, 0.93)	0.015
Other	12.7% (30/236)	1.12 (0.78, 1.62)	0.530	1.25 (0.83, 1.87)	0.291
CD4 count (cells/mm^3)					
≥350	11.1% (418/3763)	1.00		1.00	
200-349	11.4% (191/1670)	1.05 (0.89, 1.25)	0.542	1.10 (0.93, 1.30)	0.260
<200	11.3% (103/914)	1.03 (0.83, 1.27)	0.815	1.12 (0.90, 1.40)	0.307
Maternal age (years)					
21-29	10.6% (368/3473)	1.00		1.00	
≤20	13.5% (54/401)	1.28 (0.95, 1.71)	0.104	1.21 (0.90, 1.64)	0.205

30-39	11.5% (346/2999)	1.07 (0.92, 1.25)	0.361	1.15 (0.98, 1.34)	0.089
≥40	7.6% (15/197)	0.78 (0.46, 1.33)	0.368	0.92 (0.53, 1.60)	0.779
Calendar year (per increasing year)		1.00 (0.96, 1.04)	0.935	1.02 (0.97, 1.07)	0.421
Parity					
≥2	9.6% (141/1465)	1.00		1.00	
1	11.0% (269/2452)	1.19 (0.95, 1.48)	0.124	1.14 (0.91, 1.43)	0.263
0	11.8% (373/3155)	1.34 (1.09, 1.66)	0.005	1.31 (1.04, 1.64)	0.020
IDU history					
No	10.6% (669/6296)	1.00		1.00	
Yes	18.5% (84/453)	1.82 (1.46, 2.27)	<0.001	1.68 (1.33, 2.11)	<0.001
Infant sex					
Female	10.9% (377/3463)	1.00		1.00	
Male	11.3% (408/3625)	1.07 (0.92, 1.23)	0.388	1.06 (0.92, 1.22)	0.435
ART duration					
<4 weeks	9.9% (18/181)	1.00		1.00	

4-<10 weeks	14.6% (124/848)	1.69 (0.95, 2.99)	0.073	1.71 (0.97, 3.01)	0.062
≥10 weeks	10.6% (606/5730)	1.26 (0.73, 2.19)	0.400	1.36 (0.79, 2.34)	0.265
Third agent					
Other PI	8.8% (80/914)	1.00		1.00	
LPV/r	11.8% (649/5485)	1.40 (1.10, 1.80)	0.007	1.16 (0.87, 1.55)	0.323
NNRTI	7.7% (39/510)	0.98 (0.66, 1.45)	0.906	0.85 (0.56, 1.29)	0.441
PI+NNRTI /Fusion /Integrase /only NRTIs	9.4% (17/180)	0.98 (0.54, 1.77)	0.949	0.78 (0.41, 1.48)	0.455

† Adjusted also for country of delivery

References

1. UNAIDS, *On the fast-track to an AIDS-free generation. Available http://www.unaids.org/sites/default/files/media_asset/GlobalPlan2016_en.pdf, accessed June 2017*. 2016.
2. WHO, *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. 2013: Geneva, Switzerland.
3. Peters, H., et al., *UK Mother-to-Child HIV Transmission Rates Continue to Decline: 2012-2014.* Clin Infect Dis, 2017. **64**(4): p. 527-528.
4. Mandelbrot, L., et al., *No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception.* Clin Infect Dis, 2015. **61**(11): p. 1715-25.
5. von Linstow, M.L., et al., *Prevention of mother-to-child transmission of HIV in Denmark, 1994-2008.* HIV Medicine, 2010: p. 1-9.
6. Chiappini, E., et al., *Risk of perinatal HIV infection in infants born in Italy to immigrant mothers.* Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 2011. **53**(3): p. 310-3.
7. Latysheva, I. *Topical issues of prevention of mother-to-child transmission of HIV in the Russian Federation (oral presentation)*. in *International Scientific-Practical Conference on Children and HIV*. 2018. Saint Petersburg, Russia.
8. State Institution "Ukrainian Center for Socially Dangerous Disease Control of the Ministry of Health of Ukraine", *HIV Infection in Ukraine Information Bulletin, No. 45. Available at http://ucdc.gov.ua/uploads/documents/c21991/6048649d4a2a9832cba2b4df9a576be1.pdf, accessed March 2017.* 2016.
9. Bagkeris, E., et al., *Pregnancy outcomes in HIV-positive women in Ukraine, 2000-12 (European Collaborative Study in EuroCoord): an observational cohort study.* Lancet HIV, 2015. **2**(9): p. e385-92.
10. Townsend, C., et al., *Antiretroviral therapy and preterm delivery-a pooled analysis of data from the United States and Europe.* BJOG, 2010. **117**(11): p. 1399-410.
11. Fowler, M.G., et al., *Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention.* N Engl J Med, 2016. **375**(18): p. 1726-1737.
12. Chen, J.Y., et al., *Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana.* J Infect Dis, 2012. **206**(11): p. 1695-705.
13. Powis, K.M., 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**(4): p. 506-14.
14. Zash, R., et al., *Reassuring Birth Outcomes With Tenofovir/Emtricitabine/Efavirenz Used for Prevention of Mother-to-Child Transmission of HIV in Botswana.* J Acquir Immune Defic Syndr, 2016. **71**(4): p. 428-36.
15. Zash, R., et al., *Comparative Safety of Antiretroviral Treatment Regimens in Pregnancy.* JAMA Pediatr, 2017. **171**(10): p. e172222.
16. Rough, K., et al., *Birth Outcomes for Pregnant Women with HIV Using Tenofovir-Emtricitabine.* N Engl J Med, 2018. **378**(17): p. 1593-1603.
17. Nachega, J.B., et al., *Safety of Tenofovir Disoproxil Fumarate-Based Antiretroviral Therapy Regimens in Pregnancy for HIV-Infected Women and Their Infants: A Systematic Review and Meta-Analysis.* J Acquir Immune Defic Syndr, 2017. **76**(1): p. 1-12.
18. Katz, I.T., et al., *Factors associated with lack of viral suppression at delivery among highly active antiretroviral therapy-naive women with HIV: a cohort study.* Ann Intern Med, 2015. **162**(2): p. 90-9.
19. UNAIDS, *UNAIDS data and factsheets, available at http://aidsinfo.unaids.org/, accessed February 2018*. 2018.
20. Uthman, O.A., et al., *Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis.* Lancet HIV, 2017. **4**(1): p. e21-e30.

21. Villar, J., et al., *International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project.* Lancet, 2014. **384**(9946): p. 857-68.
22. Villar, J., et al., *INTERGROWTH-21st very preterm size at birth reference charts.* Lancet, 2016. **387**(10021): p. 844-5.
23. Lekhan, V., V. Rudiy, and E. Richardson, *Ukraine: Health system review*, in *Health Systems in Transition*. 2010. p. 1-183.
24. Steer, P., *The epidemiology of preterm labour.* BJOG, 2005. **112 Suppl 1**: p. 1-3.
25. Moodley, T., et al., *Improved pregnancy outcomes with increasing antiretroviral coverage in South Africa.* BMC Pregnancy Childbirth, 2016. **16**: p. 35.
26. Ransom, C.E., et al., *Infant growth outcomes after maternal tenofovir disoproxil fumarate use during pregnancy.* J Acquir Immune Defic Syndr, 2013. **64**(4): p. 374-81.
27. Favarato, G., et al., *Protease inhibitors and preterm delivery: another piece in the puzzle.* AIDS, 2018. **32**(2): p. 243-252.
28. Koss, C.A., et al., *Risk factors for preterm birth among HIV-infected pregnant Ugandan women randomized to lopinavir/ritonavir- or efavirenz-based antiretroviral therapy.* J Acquir Immune Defic Syndr, 2014. **67**(2): p. 128-35.
29. WHO, *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Second edition.* 2016: Geneva, Switzerland.
30. Papp, E., et al., *HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels, suggesting a potential mechanism contributing to fetal growth restriction.* J Infect Dis, 2015. **211**(1): p. 10-8.
31. McDonald, C.R., et al., *Estradiol Levels Are Altered in Human Immunodeficiency Virus-Infected Pregnant Women Randomized to Efavirenz-Versus Lopinavir/Ritonavir-Based Antiretroviral Therapy.* Clin Infect Dis, 2018. **66**(3): p. 428-436.
32. Gazzard, B.G. and on behalf of the Bhiva Treatment Guidelines Writing Group, *British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008.* HIV Medicine, 2008. **9**: p. 563-608.
33. French, C.E., et al., *Immunologic status and virologic outcomes in repeat pregnancies to HIV-positive women not on antiretroviral therapy at conception: a case for lifelong antiretroviral therapy?* AIDS, 2014. **28**(9): p. 1369-72.
34. Bell, J. and L. Harvey-Dodds, *Pregnancy and injecting drug use.* BMJ, 2008. **336**(7656): p. 1303-5.
35. Bailey, H., A. Turkova, and C. Thorne, *Syphilis, hepatitis C and HIV in Eastern Europe.* Curr Opin Infect Dis, 2017.
36. Sconza, R., H. Peters, and C. Thorne, *Trends in maternal characteristics of pregnancies in women living with HIV in the UK and Ireland: 2000-2015*, in *19th Annual National HIV Nurses Association Conference*. 2017: Bristol, UK.
37. Thorne, C., I. Semenenko, and R. Malyuta, *Prevention of mother-to-child transmission of human immunodeficiency virus among pregnant women using injecting drugs in Ukraine, 2000-10.* Addiction, 2012. **107**(1): p. 118-128.
38. Stoner, M.C.D., et al., *Timing of initiation of antiretroviral therapy and risk of preterm birth in studies of HIV-infected pregnant women: the role of selection bias.* Epidemiology, 2017.