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Protease inhibitors and preterm delivery: another piece in the puzzle

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Short title: Protease inhibitors and preterm delivery

Abstract

Background Questions remain regarding preterm delivery (PTD) risk in HIV-infected women on antiretroviral therapy (ART), including the role of ritonavir-boosted protease inhibitors (PI/r), timing of ART initiation and immune status.

Methods We examined data from the UK/Ireland National Study of HIV in Pregnancy and Childhood on women with HIV delivering a singleton live infant in 2007-2015, including those pregnancies receiving PI/r-based (n=4184) or non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens (n=1889).

We conducted logistic regression analysis adjusted for risk factors associated with PTD and stratified by ART at conception and CD4 count to minimise bias by indication for treatment and to assess whether PTD risk differs by ART class and specific drug combinations.

Results Among women conceiving on ART, lopinavir/ritonavir was associated with increased PTD risk in those with CD4 ≤350 (aOR 1.99[1.02, 3.85]) and with CD4>350 (aOR 1.61[1.07, 2.43]) versus women on NNRTI-based (mainly efavirenz and nevirapine) regimens in the same CD4 sub-group. Associations between other PI-based regimens (mainly atazanavir and darunavir) and PTD risk were complex. Overall, PTD risk was higher in women who conceived on ART, had low CD4 count and were older. No trend of association of PTD with tenofovir or any specific drug combinations were observed.

Conclusions Our data support a link between the initiation of ritonavir-boosted/lopinavir-based ART pre-conception and PTD in subsequent pregnancies, with implications for treatment guidelines. Continued monitoring of PTD risk is needed as increasing numbers of pregnancies are conceived on new drugs.

Keywords: drug combination; gestational age; HIV infections; lopinavir; premature birth; protease inhibitors

Introduction

It is now widely accepted that antiretroviral therapy (ART) in pregnancy is associated with increased risk of preterm delivery (PTD), but questions remain about the exact nature of this association, for example the roles of timing of ART initiation (pre- or post-conception) and maternal immunological status (e.g. CD4 count) and the extent to which specific drugs or regimens are involved in this association [1-4]. Pregnant women on protease inhibitor (PI) regimens may be at higher risk of PTD [5-8]. Limited data on mechanisms suggest that PIs may reduce progesterone levels in pregnancy [9], leading to fetal growth restriction. Progesterone may also play an important role in PTD [10, 11]. Certain antiretroviral drugs (ARV), namely ritonavir (RTV), widely used as a booster for other PI and the nucleoside "backbone" tenofovir (TDF)/emtricitabine (FTC) may also interact with PIs and increase PTD risk [12, 13]. Most recently, assessment of individual ART regimens has been recommended to better understand the differences and causes of adverse perinatal outcomes between ART [14, 15].

In a previous analysis of data from the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC) based on pregnancies delivered between 1990 and 2005 [6] we showed an increased rate of PTD in women on combination ART (cART) (14%) versus mono/dual therapy (10%). Since then, new antiretroviral drugs have been licensed and the drug combinations used routinely during pregnancy have changed substantially, with mono/dual therapy no longer used. Additionally, an increasing proportion of women are conceiving on ART [16].

In this paper we examine whether pregnant women on a regimen that includes a PI boosted with RTV (PI/r) are at higher risk of delivering preterm compared with pregnant women on an NNRTI-based regimen and whether this risk varies by ART use at conception, CD4 count (high vs low) and ART drug combination.

Methods

Study population

The NSHPC is a national surveillance study that collects comprehensive population-based data on all HIV-positive pregnant women and their children seen for care in the UK and Ireland. Information on pregnancy and delivery is collected from obstetric respondents in all maternity units, and HIV-exposed infants are followed up through their paediatrician to establish infection status. Full methodological details have been described elsewhere [17, 18]. The NSHPC has received ethical approval from the London Multi-Centre Research Ethics Committee (MREC/04/2/009).

Inclusion criteria

We included pregnancies with known gestational age resulting in a singleton live birth delivered between 2007 and 2015, in women diagnosed with HIV before delivery and reported to the NSHPC by March 2016. To investigate the association of PTD with ART class we compared pregnancies exposed to a PI/r-based regimen with those exposed to an NNRTI-based regimen and distinguished RTV-boosted lopinavir (LPV/r), the predominant PI in our study, from other PI to avoid results being driven by LPV/r. We

defined a PI/r-based regimen as a regimen that included a PI, RTV booster and two nucleoside reverse transcriptase inhibitors (NRTI) drugs (the "backbone"); similarly an NNRTI-based regimen included an NNRTI plus two NRTIs. We excluded 211 pregnancies with no or 'unspecified' data on ART, 145 with ART started <28 days before delivery and 192 pregnancies exposed to mono/dual regimens, 90 to integrase inhibitors, 77 to unboosted PI and 1510 to more than one ARV drug combination during the pregnancy. We further excluded 1371 earlier pregnancies in women with repeated pregnancies, keeping only the most recent one.

Definitions

Gestational age at delivery, in completed gestational weeks, was reported by the respondent based on expected date of delivery. We defined PTD as a delivery at <37 weeks, moderate PTD (MPTD) as delivery at 34-36 weeks and very PTD (VPTD) as delivery at <34 weeks [13]. Small for gestational age (SGA) was defined according to United States sex-specific standards [19]. Baseline CD4 cell count was defined as the first CD4 count reported in pregnancy. We grouped maternal country of origin into six main world regions according to UN classification; Western European and Western Countries+ Eastern Europe (WEWC+EE), Eastern Africa, Middle/Southern Africa, Western Africa, Caribbean (CRB) and Other.

Statistical analysis

First, we examined the overall associations of PTD with LPV/r-, other PI/r- and NNRTI-based regimens using logistic regression and multinomial logistic regression to investigate whether this association varied by MPTD and VPTD. To minimise bias by

indication for treatment we further excluded pregnancies in women with a history of injecting drug use (IDU) and those with no data on CD4 and conducted stratified analyses on four sub-groups of pregnancies: (1) no ART at conception and baseline CD4 ≤350 cell/mm^3; (2) no ART at conception and baseline CD4 >350 cell/mm^3; (3) ART at conception and baseline CD4 ≤350 cell/mm^3; (4) ART at conception and baseline CD4 >350 cell/mm^3. Finally, we investigated these associations by drug-specific regimen (rather than ART class). We included any drug combinations received in ≥5% of pregnancies and selected the combination with the lowest PTD rate as the baseline for comparison.

Analyses were adjusted for potential confounders identified *a priori* based on previous literature [6, 12, 20]: i.e. year of delivery (continuous), maternal age at delivery (divided into quartiles), parity (primiparous vs multiparous), IDU history, antenatal CD4 count (≤350 cell/mm^3, >350 cell/mm^3), ART at conception and maternal country of origin.

Results were considered statistically significant at a *p*-value of <0.05. Differences in proportions were tested for statistical significance using the chi-square test. Statistical analyses were performed using Stata version 13.1 (StataCorp, College Station, TX, USA).

Role of the 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 final dataset included 6073 pregnancies, mainly in women from sub-Saharan Africa (4445/6073, 73•2%) and of median age of 33 years (IQR 29-36); 3090 (50•9%) pregnancies were conceived on ART while the remainder started ART on average at 19•1 gestational weeks (15•7-22•1). Median CD4 count at baseline was 440 (IQR 311-596) cells/mm^3 and in 3272 pregnancies (68•5%) was above 350 cells/mm^3. Of these CD4 counts, 42•4% were measured in the first, 45•3% in the second and 12•4% in the third trimester. CD4 count was missing in 1270 pregnancies; these pregnancies tended to be at the beginning of study (*P*=0•007) but there was no difference in PTD rate (*P*=0•27) or use of ART class (*P*=0•51) compared with pregnancies with available CD4 count. PI/r-based regimens were the most common accounting for 4184 (68•9%) pregnancies, of which 2368 (39•0%) received LPV/r; the remaining 1889 (31•1%) pregnancies received a NNRTI-based (mainly efavirenz [EFV] and nevirapine [NVP]) regimen. The number of women receiving LPV/r in pregnancy was particularly high at the start of the study period but the number swiftly declined subsequently (Figure 1) due to changes in commissioning and adult treatment guidelines. Overall, the PTD rate was 10•4% (629/6073) and the VPTD rate was 3•8% (228/6073). Women receiving LPV/r had higher PTD rates than women receiving other PI/r- or NNRTI-based regimens (Table 1).

Among 5711 infants with available birthweight data, 1163 (20•4%) were SGA at delivery. Sixteen infants (0•26% of 6073), all born full-term, were HIV-infected. Ten infants (0•16%), eight of whom were VPTD, one MPTD and one full-term, died within the first 28

days. Congenital abnormalities were reported in 2•9% (171/5867) of infants. Compared to full term infants preterm infants were more likely to have a congenital abnormality (40/595 [6•7%] vs. 131/5272 [2•5%], *P* <0•001) and more likely to be SGA compared to full-term infants ([149/594] [25•1%] vs. [1014/5117] [19•8%], *P* =0•003).

After adjustment for other risk factors associated with PTD, overall analysis suggested an association of PTD with LPV/r, low CD4 count (≤350cells/mm^3), ART at conception and older maternal age (>36years) (Table 2). MPTD was associated with LPV/r and mother originating in the Caribbean VPTD and VPTD with LPV/r and IDU history (SDC Table 1, http://links.lww.com/QAD/B189).

Association of preterm delivery with ART class stratified by ART at conception and CD4 count

The highest rate of PTD (13•7%) was observed in women on ART at conception and low CD4 count (≤350 cells/mm^3) and the lowest PTD rate (8•8%) in those on ART at conception with high CD4 counts (>350 cells/mm^3) (SDC Table 2a-b). Stratified analysis suggested that irrespective of baseline CD4, PTD risk increased in women conceiving on LPV/r (Figure 2) Women who conceived on other PI/r-regimens were also at higher PTD risk when CD4 ≤350 cells/mm^3 but no clear pattern was observed when CD4 >350 cells/mm^3 (for example, PTD rates varied widely between PI/r-based regimens from 4.9% in women who conceived on RTV-boosted atazanavir [ATV/r]+ TDF/FTC to 13•4% in women who conceived on RTV-boosted darunavir [DRV/r]+ TDF/FTC).

Where ART was initiated after conception, no significant associations between PTD and LPV/r- or other PI/r-based regimens were observed irrespective of CD4 count (Figure 2). Despite exclusion from our analyses of women starting ART <28 days before delivery, some women were included who initiated ART beyond defined gestational age cut-offs for PTD (particularly very or moderate PTD) and were therefore not exposed to ART during the period that they were at risk for PTD. We therefore conducted a sensitivity analysis excluding women starting ART at ≥28 gestational weeks (n=91) but results did not vary and no significant associations were observed (SDC Table 4).

Association of preterm delivery with ART by drug combinations

Among the PI/r-regimens the most frequent combinations were LPV/r+ ZDV/3TC (1325/4698, 28·2%) and ATV/r+ TDF/FTC (535/4698, 11·4%) and among the NNRTI-regimens were EFV+ TDF/FTC (495/4698, 10·5%) and NVP+ 3TC/ABC (288/4698, 6·1%) (SDC Table 3). Thirty women with a CD4 count >350cells/mm^3 who started NVP in pregnancy were excluded from the analysis as NVP initiation is not recommended when CD4 count >250cells/mm^3.

The highest PTD rates (21·2% and 21·1% respectively) were observed in women with CD4 count ≤350 cells/mm^3, namely, in those who did conceive on LPV/r+ TDF/FTC and in those who did not conceive on ART and received DRV/r+ TDF/FTC in pregnancy.

Results from stratified analyses did not show any clear trend in PTD risk according to ART class and drug combination. Among women with CD4 count >350 cells/mm^3, PTD risk was three-fold higher when conceiving on DRV/r+ TDF/FTC or LPV/r+ TDF/FTC than when conceiving on ATV/r+ TDF/FTC. However, in women with CD4 count ≤350

cells/mm^3 PTD risk was higher in women conceiving on ATV/r+ TDF/FTC than with any other drug combinations. (Figure 3)

Discussion

In this national surveillance study, preterm births accounted for around 10% of all included singletons. An association between RTV-boosted PIs and PTD was observed but this was not consistent across all PIs. Among women who conceived on ART we found an increased risk of PTD in women on LPV/r compared with women who conceived on an NNRTI-based (mainly EFV and NVP) regimen even after taking into account other factors associated with PTD and irrespective of whether CD4 count was above or below 350cells/mm^3. The associations between other PI-based (mainly ATV/r and DRV/r) regimens and PTD risk were complex, with significant associations seen in some sub-groups but not in others. There was no trend in PTD across TDF-containing regimens, and no clear pattern when considering the most common drug combinations. Overall, PTD risk was higher in women who conceived on ART, had low CD4 count and were older (>36 years), with VPTD risk also increased in women with a history of injecting drug use.

Our findings on PTD associated with LPV/r are consistent with other studies, although there are differences. The PROMISE randomized clinical trial [10] reported significant higher PTD risk in the LPV/r+ TDF+FTC arm compared with the LPV/r+3TC/ZDV or mono ZDV+sdNVP arms although all participants initiated ART in pregnancy with CD4 count >350 cells/mm^3. Conversely, the main findings of a surveillance study in Botswana [21] suggested that PTD risk was higher in women conceiving on LPV/r+ ZDV/3TC than

in women conceiving on LPV/r +TDF/FTC, although the authors could not adjust or stratify analysis by CD4 count. When considering women with CD4>350 cells/mm^3 (Supplementary Online Content [21]) those on LPV/r+ TDF/FTC tended to have higher PTD risk than those on LPV/r+ ZDV/3TC (EFV+ TDF/FTC as the reference). It is therefore difficult to compare these results with our findings. A further study [22] that had randomised Ugandan women to LPV/r or EFV-based ART at 12-28 weeks gestation found no significant different in PTD risk between LPV/r- and EFV-based ART. In our study, the association between LPV/r and PTD was only seen among women on ART at conception, and not among those starting treatment in pregnancy.

Overall, we found that women who conceived on ART were at higher risk of PTD than those starting ART in pregnancy. The size of our dataset and availability of CD4 data meant we could stratify women who conceived on ART by CD4 group, finding that PTD rate was much higher (13·7%) in women with CD4 ≤350 than in women with CD4 >350 (8·8%). This is an important result as a recent systematic review and meta-analysis [4] that summarized findings from 11 studies showed an increased risk of PTD with pre-conception initiation of ART but authors could not differentiate between women with low and high CD4 count because of lack of data. Similarly, a very recent study using data of HIV-infected women delivering in a hospital in Malawi between 2012 and 2015 [23], a period marking the implementation of Option B+, found that women conceiving on ART were at lower risk of delivering PTD compared to those starting ART in pregnancy. However, analyses were not adjusted for CD4 count (data not available) and the Option B+ regimen did not include PIs.

The association of PTD with ART is likely to be multi-factorial. Untreated HIV infection is associated with a Th1 to Th2 immunological shift, as is normal pregnancy. As ART reverses this "normal" shift in pregnant patients with HIV [24], it has been postulated that this might be associated with increased PTD risk. Biologically this effect, altering the balance of cytokines, might be expected to have most impact where ART was initiated during pregnancy. However, the data presented here and by others [5, 1, 25] point to a greater effect of ART on PTD risk if initiated prior to conception.

Most consistent in the literature has been the association of PTD with PIs. A Canadian study [26] reported the OR of PTD with boosted PIs to be twice that of unboosted PI, raising the question of the direct impact of the booster as well as an indirect effect via higher drug concentrations. Data are lacking on the effect of full dose RTV (600mg bd) on PTD. However, a pattern emerges from our data of lower PTD with boosted ATV (100mg RTV daily) compared with LPV (100mg RTV bd) and darunavir (RTV 100mg daily or bd). In the PROMISE study [13] LPV/r dose was increased for the third trimester resulting in exposure to RTV 150mg twice daily. We excluded women on unboosted PIs from our analysis, as the small number precluded statistical comparison with other groups; the PTD rate in this group was 5·2%. PIs are associated with reduced levels of progesterone [9], possibly by reducing prolactin levels and increasing placental expression of the prolactin-regulated, progesterone-inactivating enzyme 20-α-hydroxysteroid dehydrogenase (20α-HSD) [27] and a study of topical cervical progesterone in HIV has been proposed to explore whether this improves perinatal outcomes [11], but it is clear that more research is needed, including to understand the effect of PI exposure throughout pregnancy on progesterone levels. The PROMISE study

focused attention on the role of nucleosides/nucleotides; one interpretation of the PROMISE results is that TDF/FTC is associated, at least when administered with LPV/r, with increased PTD risk. In our study an increased PTD risk was seen when TDF/FTC were administered with LPV/r but not with ATV/r (possibly due to lower ATV/r concentrations with TDF) nor with NNRTIs, suggesting that TDF/FTC *per se* are not associated with PTD risk. An alternative hypothesis could be that ZDV-based therapies are associated with lower risk of PTD, supported by data from the PROMISE [13] and Mma Bana [7] studies (ABC/ZDV/3TC) and by data from the NSHPC on ZDV monotherapy and ZDV/3TC dual therapy [2]. In another clinical trial conducted in Uganda the backbone to both arms (EFV v LPV/r) was ZDV+3TC, with no significant difference in PTD observed (16·2% with LPV/r v 14.7% with EFV) [22]. Finally, restoration of immune function with treatment may unmask otherwise hidden risks for PTD. A resurgence in risk of pre-eclampsia has been reported in the cART era, whereas mothers on ZDV monotherapy had lower than expected rates [28]. This might be considered a form of immune reconstitution inflammatory syndrome (IRIS), and would not necessarily be class-specific, as such an effect would correlate with overall regimen efficacy.

The size of the NSHPC dataset allowed us to stratify analyses by CD4 count and ART at conception to minimize bias in treatment indication, as well as to investigate PTD risk associated with the most commonly prescribed regimens in the UK between 2007 and 2015. However, our study had some limitations. There was some systematic bias as we excluded *a priori* women exposed to ART for <28 days before delivery. In this group the PTD rate was extremely high (42/145, 29·0%) and the reasons behind this are likely to be

complex and deserve separate investigation. We could not adjust for maternal HIV disease stage prior to conception or nadir CD4 count (because data not collected by NSHPC) or other co-infections, which may increase the risk of PTD or determine ART regimen choice. Until recently, ART was prescribed outside of the context of pregnancy to women with immune deficiency and/or low CD4 count. Women starting treatment before conception in earlier years were more likely to have started because of HIV disease, and may therefore have risk factors for adverse pregnancy outcome not present in women first starting ART during pregnancy [15, 16]. This scenario (and thus residual confounding) may be particularly relevant to women who conceived on LPV/r (as LPV/r was more frequently prescribed in earlier years of the study) and DRV/r. DRV-based regimens were recommended second-line in UK guidelines between 2008 and 2012, implying higher prevalence of previous severe maternal HIV disease and/or virological failure. Pregnant women living with HIV in the UK/Ireland have risk factors for PTD in common with the general population, such as such as older maternal age and injecting drug use, or coming from communities at increased PTD risk, such as women originating in the Caribbean [29]. However, we were not able to adjust our analyses for other important PTD risk factors such previous PTD, maternal body mass index, smoking and socio-economic status because the NSHPC does not collect this information.

Our data support a link between the initiation of LPV/r-based ART prior to pregnancy and subsequent PTD, which should be factored into treatment guidelines. Although rarely prescribed in the UK now, LPV/r-based regimens are still used by large numbers of pregnant women living with HIV in Eastern Europe [30, 31]. Our findings also show increased PTD risk among women on other specific regimens at conception with CD4

counts above 350 cells/mm^3. This is of particular relevance given the rapid growth in the number of women with HIV conceiving on ART expected in lower and middle income settings with current guidelines to initiate ART at any CD4 cell count [32], and the implications of PTD for infant morbidity and mortality in such settings [33]. The public health approach to HIV treatment in lower and middle income settings precludes an individualized approach to ART according to women‟s childbearing potential/intent and PTD risk, and the safest regimens for all women therefore need to be identified and included in guidelines.

Conclusions

Our data support a link between the initiation of RTV-boosted/LPV-based ART pre-conception and PTD in subsequent pregnancies. These, and other data associating the pre-conception choice of ART with pregnancy outcomes have implications for adult and not just pregnancy treatment guidelines given that increasing numbers of pregnancies worldwide are conceived on ART [34]. Although the benefits of ART for pregnant women living with HIV and their infants are clear, data on safety and pharmacokinetics in pregnancy are lacking, particularly for newer drugs and classes and continued monitoring of PTD risk is needed.

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Conflicts of interest

CT and PT have received funding from AbbVie; CT has received funding from ViiV and participated in an Advisory Board for ViiV. CTo has received consultancy fees from WHO and Public Health England. The other authors have no conflicts of interest to disclose.

Author contributions

Conceptualization: GF, CTo, CT, PT, HB; Data curation: HP; Formal analysis: GF; Funding acquisition: CT, PT; Investigation: GF, CTo, HB, HP, PT, GT, CT; Writing – original draft preparation: GF, CTo, CT, GT; Writing – review and editing: GF, CTo, HB, HP, PT, GT, CT.

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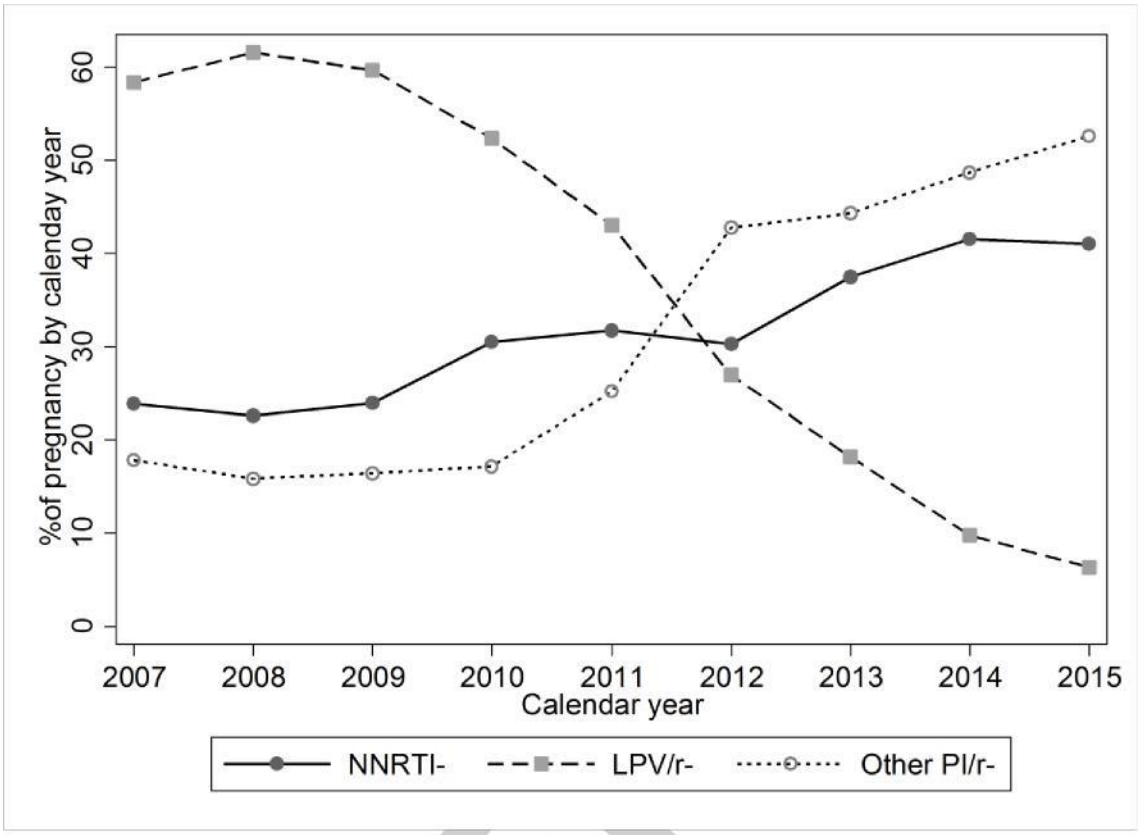

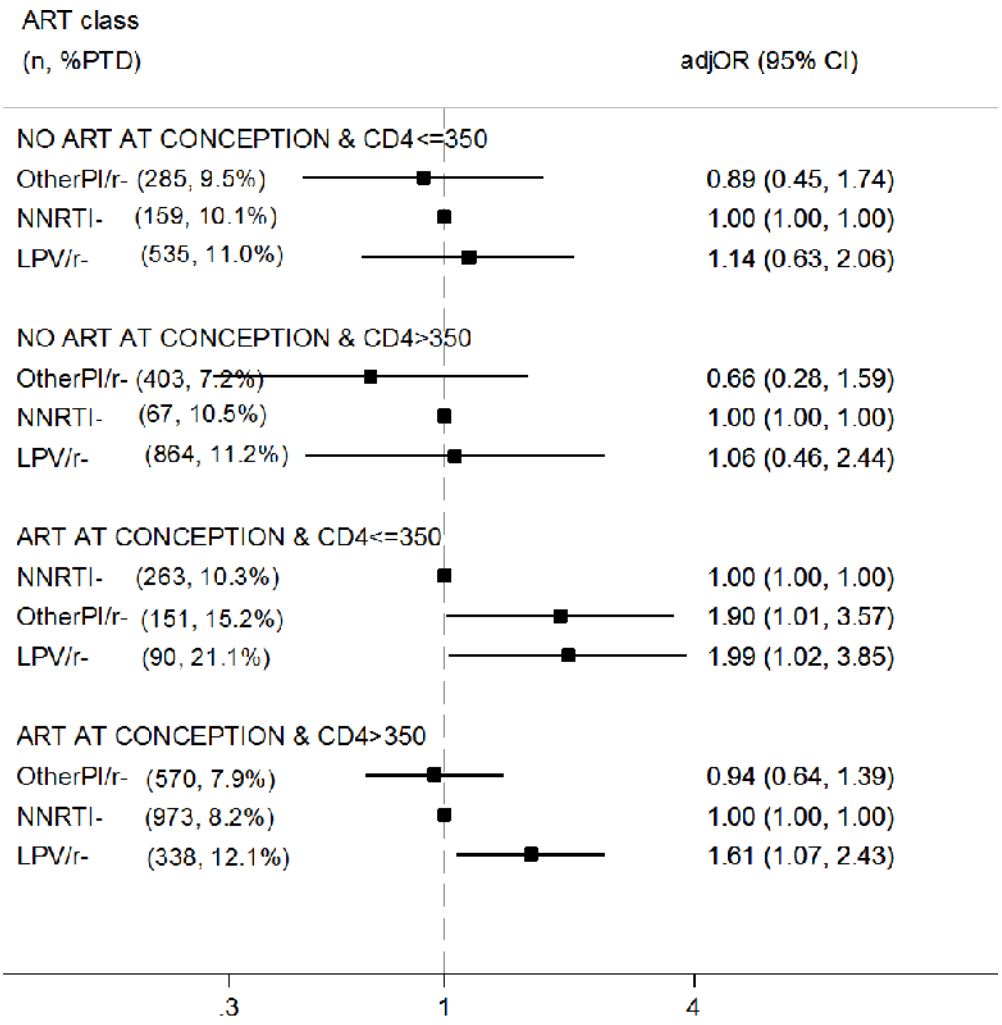

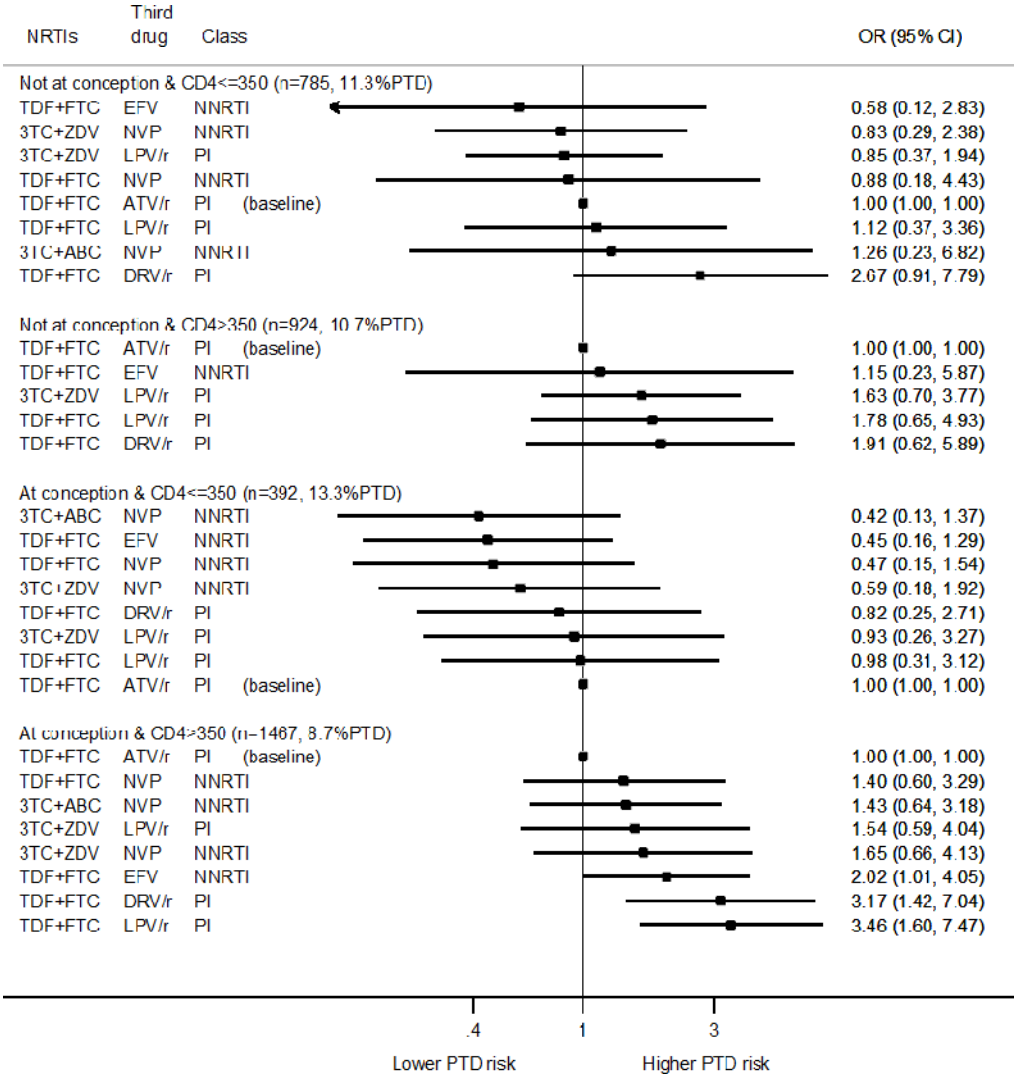

Table 1 Characteristics of all pregnancies by NNRTI-, LPV/r- and other PI-based regimens.

	NNRTI+2NRTI	LPV/r+2NRTI	Other PI/r+2NRTI	
	N (%)	N (%)	N (%)	
	1889 (31.1)	2368(39.0)	1816(29.9)	***P*-value[a]**
PTD (<37 GW)	169(9.0)	284(12.0)	176(9.7)	0.003
MPTD (3634 GW)	98(5.2)	191(8.1)	112(6.2)	
PTD (<34 GW)	71(3.8)	93(3.9)	64(3.5)	
Year of Delivery				<0.001
20072009	466(24.7)	1192(50.3)	338(18.6)	
20102012	704(37.3)	952(40.2)	637(35.1)	
20132015	719(38.1)	224(9.5)	841(46.3)	
Maternal age at delivery				<0.001
<28 years	305(16.2)	724(30.6)	430(23.7)	
2832 years	415(22.0)	644(27.2)	455(25.1)	
3336 years	575(30.4)	568(24.0)	475(26.2)	
>36 years	594(31.5)	432(18.2)	456(25.1)	
Years since HIV diagnosis	6.0(3.48.5)	2.6(0.55.6)	5.2(2.08.4)	<0.001[b]
Regions of origin				<0.001
WEWC+EE	263(13.9)	495(20.9)	389(21.4)	
East Africa	934(49.4)	1003(42.4)	681(37.5)	
West Africa	309(16.4)	369(15.6)	357(19.7)	
Mid/South Africa	239(12.7)	305(12.9)	237(13.1)	
Caribbean	44(2.3)	45(1.9)	41(2.3)	
Other	100(5.3)	151(6.4)	111(6.1)	

Parity (n=5945)				
Primiparous	506(26.8)	743(31.4)	535(29.5)	<0.001
Multiparous	1330(70.4)	1615(68.2)	1216(67.0)	
History of IDU	14(0.7)	44(1.9)	47(2.6)	<0.001
Baseline CD4 (cells/mm^3) (n=4377)				0.016
CD4>350	1047(71.1)	1225(65.9)	1000(69.3)	
CD4 350	426(28.9)	635(34.1)	44(30.8)	
Median(IQR)	456(325610)	430(303582)	441 (317605)	0.004 [b]
ART at conception	1577(83.5)	565(23.9)	948(52.2)	<0.001
Mode of delivery				<0.001
Vaginal	765(41.0)	930(39.5)	779(43.6)	
Emergency CS	500(26.8)	555(23.6)	462(25.9)	
Elective CS	601(32.2)	868(36.9)	544(30.5)	
Small for gestational age	338 (19.2)	494 (21.6)	331 (19.9)	0.15
Birthweight (g) median(IQR)	3090 (27003430)	3020 (27003380)	3062 (26203440)	0.19 [b]

PTD= preterm, MPTD= moderate preterm, VPTD= very preterm, WEWC + WW= Western Europe (UK/Ireland excluded) and Westernised countries + Eastern Europe, IDU= intraveneous drug use, CS= Caesearian Section.

[a] *p* value for Chi square test unless stated; [b] *p* value for Kruskal Wallis test.

Table 2 Associations of PTD with NNRTI-, LPV/r- and other PI-based regimens

	N	PTD %	Unadjusted OR (95%CI)	Adjusted OR[a] (95%CI)
	6073	10.4		
ART class in pregnancy				
NNRTI+2NRTI	1889	9.0	1.00	1.00
LPV/r+2NRTI	2368	12.0	1.39 (1.13,1.70)	1.56 (1.19,2.04)
Other PI/r+2NRTI	1816	9.7	1.09 (0.88,1.36)	1.10 (0.84,1.45)
Delivery year (per 1 year increase)[b]			0.95 (0.92, 0.98)	0.96 (0.92,1.01)
20072009	1996	11.6	.	.
20102012	2293	10.2	.	.
20132015	1784	9.3	.	.
Maternal age at delivery				
<28years	1459	9.9	1.00	1.00
2832years	1514	10.9	1.12 (0.88,1.41)	1.23 (0.92,1.63)
3336years	1618	9.3	0.93 (0.73,1.19)	1.12 (0.84,1.50)
>36years	1482	11.5	1.18 (0.94,1.50)	1.41 (1.05, 1.89)
Maternal origin				
WEWC+EE	1147	12.1	1.40 (1.03,1.90)	1.34 (0.94, 1.93)
East Africa	2618	10.1	1.14 (0.87,1.51)	1.08 (0.79,1.49)
West Africa	1035	9.7	1.09 (0.79,1.50)	1.08 (0.75, 1.57)
Mid/Southern Africa	781	9.0	1.00	1.00
Caribbean	130	14.6	1.74 (1.01,3.00)	1.83 (0.98, 3.40)
Other	362	9.9	1.12 (0.73,1.71)	1.05 (0.63,1.73)
Parity[c]				

Primiparous	1784	10.8	1.00
Multiparous	4161	10.1	0.93 (0.78,1.11)
History of IDU			
No	5968	10.2	1.00
Yes	105	17.1	1.81 (1.08,3.03)
ART at conception			
No	2983	10.5	1.00
Yes	3090	10.2	0.96 (0.82,1.14)
First antenatal CD4 count[c]			
>350 cells/mm^3	3272	9.5	1.00
≤350 cells/mm^3	1505	11.5	1.24 (1.