dolutegravir-based regimens at the time of conception. Of note there have been no reported neural tube defects in infants born to a further 2812 women in the Botswana study who started dolutegravir during pregnancy, including in the first trimester [39].

Further analysis of prospective surveillance data on 1908 women from the Tsepamo study in Botswana was presented at AIDS 2020 [40]. These women were on dolutegravir-based ART regimens at the time of conception and seven neural tube defects were reported (0.20%), down from 0.9% in original data in published in 2018 [41]. This compares to a rate of neural tube defects of 0.11% in women who conceived on non-dolutegravir-containing ART, and 0.07% in those taking efavirenz-containing regimens at the time of conception. The greater number of conceptions on dolutegravir in this analysis provides a more precise estimate with further narrowing of confidence intervals (CIs) (95% CI 0.09–04) than the initial data, and shows a smaller difference in incidence of neural tube defects between exposure to dolutegravir at conception and exposure to other ART.

Two other studies recently reported neural tube defect rates in infants exposed to dolutegravir at conception [42]. A neural tube defect surveillance study, also conducted in Botswana, reported a neural tube defect rate of 0.66% in 152 dolutegravir-exposed pregnancies and a retrospective analysis from Brazil reported no neural tube defects among infants born to 382 women who conceived on dolutegravir [43]; the overall rate of neural tube defects in Brazil is <0.06%. Furthermore, the most recent update from the APR showed that among 248 dolutegravir exposures at conception there was one neural tube defect giving a prevalence of 0.40% [44]. However, this estimate is based on a single neural tube defect among a relatively small number of exposures.

Furthermore the IMPAACT 2010 study compared the safety and virological efficacy of dolutegravir + emtricitabine/tenofovir alafenamide versus dolutegravir + emtricitabine/tenofovir DF versus efavirenz/emtricitabine/tenofovir DF in pregnant women as described in detail in section 6.3.2 [13]. Pregnancy outcomes for 640 women (99.5%) showed fewer women in the dolutegravir + emtricitabine/tenofovir alafenamide arm (24.1%) had an adverse pregnancy outcome than in the dolutegravir + emtricitabine/tenofovir DF (32.9%; *P*=0.043) or efavirenz/emtricitabine/tenofovir DF (32.7%; *P*=0.047) arms. Although stillbirth occurred more frequently with dolutegravir + emtricitabine/tenofovir alafenamide (3.7%) and dolutegravir + emtricitabine/tenofovir DF (5.2%) than efavirenz/emtricitabine/tenofovir DF (1.9%) (*P*-values ≥0.05; post-hoc), all cases were reviewed by investigators and not deemed to be due to investigational agents (Waitt C, personal communication). Neonatal death occurred less frequently in both dolutegravir-containing arms (dolutegravir + emtricitabine/tenofovir alafenamide [1.0%; *P*=0.019], dolutegravir + emtricitabine/tenofovir DF [1.5%; *P*=0.053) and efavirenz/emtricitabine/tenofovir DF [4.8%]).

The writing group recognises that incidence of neural tube defects varies between countries and not all countries have introduced folic acid fortification.

The World Health Organization has updated recommendations for first-line treatment regimens to include dolutegravir, in combination with an NRTI backbone, as preferred first-line treatment for people living with HIV, including women of child-bearing potential. This decision was taken in the context of the potential risks of negative aspects of other ART choices [45].

The writing group agrees that all women living with HIV should be given all available information and supported to make informed choices regarding ART, at all stages of their reproductive life.

Based on these findings the writing group makes the following recommendations:

1. **For a woman on dolutegravir wishing to conceive:**
    a. Women should be fully informed that the prevalence of neural tube defects is higher following dolutegravir exposure at conception than with other types of ART at conception (equating to 2 per 1000 births *vs* 1 per 1000 births).
    b. The best safety data in pregnancy are for efavirenz or atazanavir/r and these should be considered first line in pregnancy.
    c. All women choosing to continue dolutegravir while planning to conceive will be supported in this decision and advised to commence or continue folic acid 5 mg od based on the original Medical Research Council data on prevention of neural tube defects in the general population [46].
2. **For a woman on dolutegravir who becomes or is pregnant:**

a. We acknowledge the neural tube has closed within 6 weeks of conception but the mechanism of some of the reported abnormalities remains uncertain. If dolutegravir is the best ART choice for the woman, the neural tube defect risk of 0.20% should be discussed and if a woman accepts this risk then dolutegravir can be continued in pregnancy.

b. We do not recommend switching from dolutegravir if the pregnancy is confirmed to be already past 6 weeks' gestation unless there are other reasons to consider switching.

c. If the physician/woman choose(s) to switch, use a regimen for which there are the most safety data in pregnancy, such as efavirenz or atazanavir/r.

d. Detailed anomaly scans should be performed as per national pregnancy guidelines with no additional scans required.

Historical recommendations that efavirenz be avoided in women who may conceive [47] were based on preclinical animal studies that had not been conducted on any other ART, the US Food and Drug Administration (FDA) reclassification of efavirenz to category D, and the paucity of human data. Based on current evidence, the writing group recommends that efavirenz can be used (i.e. both continued and commenced) in pregnancy without additional precautions and considerations above those of other antiretroviral agents [48].

For further information on toxicity and pharmacokinetics and discussion regarding choice of ART, see section 6.7.

6.6 Preterm delivery (PTD)

Rates of PTD in women with HIV are high. This was the case prior to cART and remains so in the current era. However, data on the association between PTD and different antiretroviral agents are complex. Some studies, but not all, implicate boosted PIs. Particularly in observational studies, differences between populations and timing of cART initiation undoubtedly contribute to the discrepant findings, while data on other risks associated with PTD including previous PTD are rarely collected. However, while the early studies investigated women initiating cART in pregnancy it is also becoming apparent that women conceiving on cART, with an undetectable HIV load, still have a higher than expected PTD rate.

Studies showing no association between boosted PIs and PTD

Several large observational studies from the USA have not found an association between cART and PTD [49,50]. A US meta-analysis in 2007 did not find an association between PI-containing cART and PTD [51], and analysis of the NSHPC UK and Ireland data, although demonstrating the increased risk of PTD in women on cART, similarly did not find a difference when comparing PI- and NNRTI-based regimens [52]. In addition, an analysis of data on over 10,000 women reported to the APR from 1989 to 2010 did not find a significant increase in PTD in women with PI exposure with lower pre-existing risk [53]. Over 85% of these reports to the APR came from the USA.

Most studies that have examined the relationship between the timing of cART initiation and PTD have found that the risk was increased in those either conceiving on cART or taking it early in pregnancy (in the first trimester) [51,54-56]. However, an NSHPC UK and Ireland study did not find an association between timing of cART initiation and PTD [52]. A 2010 US study attempted to overcome the potential confounding factors associated with timing of cART initiation by including only women starting cART in pregnancy and comparing PI-containing with non-PI-containing regimens and did not find an association between PI-containing regimens and PTD [57]. In this study, 72% of the 777 women received a PI-based regimen, and in 47% of those the PI was nelfinavir with 22% on lopinavir/r. Further comparison between nelfinavir and lopinavir/r was unfortunately not possible. A small Canadian study retrospectively reviewed 384 women living with HIV compared to a matched HIV-negative cohort [58]. A two-fold increase in preterm birth, low birth weight and small for gestational age parameters was found, however no statistical difference between the two cohorts remained when odds ratio was adjusted for race and history of PTD.

Studies suggesting an association between boosted PIs and PTD

The association between cART and PTD was first reported by the Swiss Cohort study group in 1998 [59], and subsequently from a number of other European studies including three analyses from the European Cohort Study [54,56,60,61]. Analysis of the NSHPC UK and Ireland data in 2007 found that there was a 1.5-fold increased risk of PTD when comparing women on cART with those on monotherapy or dual therapy [52]. One single-centre UK study found the risk was increased in women initiating cART in pregnancy compared to those conceiving on treatment [62].

In two US studies, one multicentre study from the Pediatric Spectrum of HIV Disease cohort and one single-centre study, an association between cART and PTD was found only if cART included a PI [63,64]. Two of the earlier European Cohort Study reports had also noted that the increased risk of PTD in patients on cART was particularly marked in patients on PI-containing cART [54,56].

A 2011 study from the ANRS reported an association between cART and PTD and in the 1253 patients initiating a PI-based regimen, those on ritonavir-based PI regimens were significantly more likely to deliver prematurely compared to those on a non-boosted PI regimen (hazard ratio 2.03; 95% CI 1.06–3.89) [65]. One additional analysis from the APR of 955 live births exposed to lopinavir/r reported a PTD rate of 13.4% [66]. A retrospective study from the UK reported a PTD rate of 10% in 100 women taking atazanavir/r in pregnancy, of whom 67% had conceived on their regimen [67]. The same group found no difference in PTD rates in a retrospective study comparing lopinavir/r and atazanavir/r as the third agent in cART [68]. The latest publication from the NSHPC suggests that atazanavir/r has a lower PTD rate than lopinavir/r, particularly in women with a CD4 count <350 cells/mm^3 and compared to darunavir/r in women initiating cART in pregnancy [69].

Several randomised studies investigating the use of different antiretroviral regimens in different settings have now been published, although none was designed specifically to address whether ART affects the rate of PTD. The Mma Bana study from Botswana randomly allocated 560 women at 26–34 weeks' gestation, with CD4 cell counts >200 cells/mm^3, to receive either lopinavir/r plus zidovudine/lamivudine (PI group) or abacavir/zidovudine/lamivudine (NRTI group). The PTD rates were significantly higher in the PI group (21.4% *vs* 11.8%; *P*=0.003) [70]. A second study, the Kesho Bora Study, randomly allocated 824 women at 28–36 weeks' gestation, again with CD4 cell counts >200 cells/mm^3, to receive either lopinavir/r with zidovudine/lamivudine or zidovudine monotherapy twice daily plus a single dose of nevirapine at the onset of labour. There was no difference in the PTD rate between the two groups (13% with PI *vs* 11% with zidovudine monotherapy/single-dose nevirapine) [71]. An analysis of placental malaria data from PROMOTE of 391 Ugandan women randomly assigned to lopinavir/r or efavirenz initiated during pregnancy showed no significant difference in PTD: 15.9% and 13.6%, respectively [72]. Finally, in the PROMISE study lopinavir/r prescribed with tenofovir DF/emtricitabine was associated with a high neonatal mortality rate due to severe PTD, which was not seen with lopinavir/r when prescribed with zidovudine/lamivudine, nor with zidovudine monotherapy. However, in both PI arms the doses of lopinavir and ritonavir were increased by 50% for the duration of the third trimester. A role for ritonavir has been proposed – PTD is not associated with nelfinavir (no ritonavir) or with atazanavir/r (100 mg ritonavir), and is most strongly associated with lopinavir (usually 200 mg daily; 300 mg daily in PROMISE).

Summary

The data regarding cART, including individual components of cART, and PTD remain complex and it is likely that there are several drivers. The most consistent findings suggest lopinavir/r should be avoided, while the latest UK data favour atazanavir/r if a PI is indicated. Randomised controlled trial data on the current most commonly prescribed boosted PIs in the UK are not available thus the NSHPC data provide the best guide. Additional data on once daily darunavir/r would be helpful. A patient friendly, approach to assessing the data has been developed by the BMJ guidelines group [73].

Of note, recent reports on the pharmacokinetic profiles of cobicistat and the safety concerns over dolutegravir exposure during the first few weeks of gestation demonstrate that the newest therapies may not be the safest in pregnancy and that older 'tried and tested' regimens may still be preferred, considering that a woman with fully suppressed HIV on therapy has a very low risk of vertical transmission regardless of the combination. Therefore safety in pregnancy becomes the most pressing concern. The importance and long-term impact of PTD, even with access to excellent neonatal care, should not be underestimated.

6.7 Pharmacokinetics of antiretrovirals in pregnancy

6.7	No routine dose alterations are recommended for antiretrovirals during pregnancy if used at standard adult licensed doses, apart from raltegravir, which should be given as 400 mg bd.	1C
	Consider TDM particularly if combining tenofovir DF and atazanavir/r.	2C
	If dosing off licence, consider switching to standard dosing throughout pregnancy or regular TDM.	2C

Physiological changes that occur even during the first trimester of pregnancy may affect the kinetics of drug absorption, distribution, metabolism and elimination, thereby affecting drug dosing [74]. In pregnancy, gastrointestinal pH is increased, transit time becomes prolonged, body water and fat increase, and there are accompanying increases in cardiac output, ventilation and liver and renal blood flow. Plasma protein concentrations decrease, notably albumin and α1 acid glycoprotein; renal sodium reabsorption increases and changes occur in the metabolic enzyme pathway in the liver, including changes in cytochrome P450.

6.7.1 NRTIs

The pharmacokinetics of most NRTIs (zidovudine [75], lamivudine [76] and abacavir [77]) are not significantly altered by pregnancy and dose adjustment is not required.

Tenofovir DF concentrations in the third trimester were reported to be reduced by about 15–25% compared with postpartum, but trough levels were adequate [78,79]; however in a population-based study of tenofovir DF use, clearance in pregnant women appeared to be 39% higher than in non-pregnant women [80]. Higher rates of treatment failure during pregnancy with tenofovir DF-containing combinations have not been reported. Another study reported lower tenofovir DF area under the curve (AUC) and trough levels throughout pregnancy and found that this was linked to higher maternal weight. One double dose of tenofovir DF administered shortly before delivery resulted in plasma concentrations similar to those observed in non-pregnant adults following a standard 245-mg dose and adequate levels in the neonate [26,81] (see section 9). A review of antenatal patients with HIV attending a London hospital showed no decline in renal function during pregnancy in women taking tenofovir DF.

Tenofovir alafenamide is a newer version of tenofovir DF and although data on the safety and pharmacokinetics of tenofovir alafenamide are limited, no signals for concern with regard to birth defect have been reported [82]. However, the writing group does not recommend its routine use in pregnancy until further data are available. This should be discussed with all women who conceive on tenofovir alafenamide, and consideration should be given to switching to an alternative NRTI regimen.

Data on emtricitabine show that while third-trimester concentrations are lower than postpartum the absolute concentrations achieved during pregnancy are adequate and dose adjustment is not required [79,83].

6.7.2 NNRTIs

Rilpivirine is recommended in the current BHIVA Adult Treatment Guidelines [5] as a first-line antiretroviral agent with tenofovir DF and emtricitabine in patients with viral load <100,000 HIV RNA copies/mL. A pharmacokinetic study by the PANNA consortium [84] carried out intensive 24-hour pharmacokinetic profiles in women living with HIV receiving rilpivirine 25 mg od in the third trimester and postpartum. Fifteen women were included in the study and rilpivirine levels were approximately 50% lower during the third trimester than postpartum. However, all women had <50 HIV RNA copies/mL at delivery and there were no vertical transmissions. Based on this, it is recommended that women may be commenced or continued on rilpivirine-containing regimens (with no routine dose adjustment) if they are able to take their medication with a meal to optimise pharmacokinetics, and that they are closely monitored with additional viral load monitoring and TDM if clinically indicated.

Efavirenz 600 mg od was reported in one study of 25 pregnant women to result in third-trimester plasma concentrations that were similar to 6- to 12-week postpartum concentrations. Cord blood to maternal blood ratio was 0.49 resulting in transplacental concentrations in the therapeutic range [85].

A study of the pharmacokinetics of etravirine 200 mg bd in 15 women found an increase in etravirine exposure during pregnancy but still within the range observed in previous studies of non-pregnant individuals with HIV treated with this dose [86]. Fourteen of 15 women had an undetectable viral load during pregnancy and no vertical transmissions were reported. A second study from the PANNA group has shown similar findings [87].

Nevirapine has been extensively investigated in pregnancy and plasma concentrations are similar to those in non-pregnant adults [21,88]. No dose adjustment is required when using licensed doses. There are no data on the prolonged release formulation of nevirapine in pregnant women and therefore consideration should be given to switching patients on 400 mg prolonged release formulation to the 200 mg bd formulation during pregnancy. It should be noted that nevirapine is no longer a preferred treatment option for naïve patients in the current BHIVA Adult Treatment Guidelines [5].

6.7.3 Integrase inhibitors

Raltegravir 1200 mg od should not be used in pregnancy. Instead a woman should be switched to or started on 400 mg bd.

A study of pregnant women taking raltegravir 400 mg bd found adequate trough levels in all 10 women in the study, although levels were very variable and lower than postpartum [87]. In another study of five women, third-trimester concentrations were no lower than postpartum and in the two cord blood samples studied, the cord blood to maternal blood ratio was >1.0 [89]. A third study of 23 women receiving raltegravir 400 mg bd, mostly as intensification of PI-based regimens during pregnancy, showed no statistically significant change in raltegravir concentrations during pregnancy and postpartum [90]. The PANNA study has also shown similar results [91]. In an ongoing prospective study of 31 women who took raltegravir during pregnancy, mostly (74%) starting in the third trimester, no evidence of adverse events has been observed in infants who are being followed up to 6 years [92].

The IMPAACT P1026s study is an ongoing prospective study of antiretroviral pharmacokinetics in pregnant women living with HIV [93]. Results from intensive 24-hour pharmacokinetic profiling for elvitegravir and cobicistat in women during the second and third trimesters and postpartum have been reported. Twenty-nine subjects were included and elvitegravir and cobicistat exposures were lower and clearance higher during pregnancy, compared to postpartum. Viral load at delivery was <50 HIV RNA copies/mL for 14/19 women (74%). Congenital abnormalities were reported in two infants. Analysis of elvitegravir and cobicistat levels in infant blood showed undetectable levels of cobicistat and a similar elvitegravir elimination half-life for infants in comparison to adults. In view of recent data on darunavir/cobicistat in pregnancy, cobicistat-boosted regimens are not recommended in pregnancy.

The IMPACT 1026 trial has also assessed maternal dolutegravir pharmacokinetics and showed that the calculated dolutegravir AUC was 25–30% lower in the second and third trimesters but not statistically significantly different to the AUC during the postpartum period. The AUC was also numerically similar to the value in non-pregnant adults. Therefore no dose adjustment is required [94].