	baseline viral load of 30,000–100,000 HIV RNA copies/mL; • Within the first trimester if viral load >100,000 HIV RNA copies/mL and/or CD4 cell count is less than 200 cells/mm^3. All women should have commenced cART by week 24 of pregnancy.	

When determining the optimal time to start cART, the following must be considered:

- The theoretical issues for avoiding medication during pregnancy, in particular the first trimester;
- Evidence of risk of congenital abnormality following exposure to cART (see section 6.5);
- Maternal health;
- Risk of vertical transmission to the infant as determined by maternal viral load, whether cART is taken in pregnancy, and the time on cART prior to delivery.

Major determinants of a woman suppressing to a viral load <50 HIV RNA copies/mL by the time of delivery are the baseline untreated viral load and the time available to achieve this target. In both the UK and Ireland, and also the ANRS French Perinatal Cohort, vertical transmission was significantly associated with starting treatment later in pregnancy. In the French cohort, the median duration of treatment was 9.5 weeks among women where vertical transmission occurred, compared with 16 weeks for non-transmission (*P*<0.001) [9]. NSHPC data also show an increased risk of transmission in those initiating treatment beyond 30 weeks, compared to those starting earlier [10].

In the Mma Bana study, plasma HIV viral load at delivery <400 HIV RNA copies/mL was observed in 96% (lopinavir/r-based therapy) and 100% (abacavir/lamivudine/zidovudine) of women with baseline plasma viral load <1000 HIV RNA copies/mL, and in 86% (lopinavir/r-based therapy) and 90% (abacavir/lamivudine/zidovudine) with a baseline viral load >100,000 HIV RNA copies/mL. When therapy was initiated at 31–34 weeks, viral suppression was seen in only 78% of women on PI-based therapy [11].

Data from a UK multicentre study retrospectively analysing outcomes in pregnant women initiating cART at a median gestation of 23 weeks demonstrated very low rates of virological suppression in women with a baseline viral load in the upper quartile (>32,641 HIV RNA copies/mL) with only 46% achieving <50 HIV RNA copies/mL by 36 weeks' gestation (the time point used to make most delivery management decisions); this fell to 37% for baseline viral loads >100,000 HIV RNA copies/mL [12]. For all viral loads >10,000 HIV RNA copies/mL, treatment initiation later than 20.3 weeks' gestation was associated with significantly reduced likelihood of successful viral load suppression.

Therefore, the writing group recommends that cART should be commenced as soon as possible in women with baseline viral load >100,000 HIV RNA copies/mL, and at the start of the second trimester, or as soon as possible thereafter, in women with a baseline viral load between 30,000 and 100,000 HIV RNA copies/mL.

Deferring treatment to the start of the second trimester may be necessary if the woman is experiencing nausea and/or vomiting of pregnancy. However, where she is at risk of or has presented with an opportunistic infection, initiation of cART should not be delayed because of pregnancy, to protect both maternal and fetal health.

All women should have commenced cART by week 24 of pregnancy.

In women with a history of preterm delivery (PTD) it may be prudent to start cART as soon as possible after the first trimester to maximise time on cART prior to delivery although there are no supporting data and avoidance of PIs associated with PTD may be considered (see section 6.6).

6.3 Woman is not already on cART: what to start

6.3.1	Women are recommended to start tenofovir DF or abacavir with emtricitabine or lamivudine as a nucleoside backbone.	2C
6.3.2	It is recommended that the third agent in cART should be efavirenz or atazanavir/r, as these are agents with the most safety data in pregnancy.	1C
	Rilpivirine (25 mg od), raltegravir (400 mg bd) or darunavir/r (600/100 mg bd) may be used as	1C

	alternatives.	
	Darunavir/r should be prescribed at the twice daily dose (600/100 mg bd) if known resistance, and consideration should be given to using this higher dose if darunavir is initiated in pregnancy.	2C
	Dolutegravir (50 mg od) may be considered from 6 weeks' gestation which must be confirmed.	1C
	Zidovudine monotherapy is not recommended and should only be used in women declining cART with a viral load of <10,000 HIV RNA copies/mL and willing to have a caesarean section (CS).	1A
	Tenofovir alafenamide may be prescribed for women after the first trimester of pregnancy	1C
	PI monotherapy, darunavir/cobicistat and elvitegravir/cobicistat are not recommended in pregnancy.	1C

There is good evidence for the use of efavirenz in pregnancy; however, it is no longer a preferred regimen for ART-naïve patients in BHIVA and international guidelines for treatment of HIV in adults. It may be prescribed to a pregnant woman for the duration of her pregnancy with a subsequent switch postpartum. Rilpivirine may be considered as an alternative.

Ritonavir-boosted PIs are robust and may be employed where there are concerns about adherence. Atazanavir/r is recommended over darunavir/r and lopinavir/r which have an increased risk of preterm delivery.

Raltegravir may also be used but must be dosed at 400 mg bd as there are no pharmacokinetic data to support the use of 1200 mg od in pregnancy.

Dolutegravir is discussed in detail in section 6.5 and can be used only from 6 weeks' gestation (which must be confirmed) until further data on the use of dolutegravir in pregnancy become available.

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 [13]. Overall, 643 pregnant women with HIV in nine countries were randomly assigned 1:1:1 to start open-label dolutegravir + emtricitabine/tenofovir alafenamide (*n*=217), dolutegravir + emtricitabine/tenofovir DF (*n*=215) or efavirenz/emtricitabine/tenofovir DF (*n*=211) at 14–28 weeks' gestational age. Safety outcomes compared between all arms were:

(i) composite adverse pregnancy outcome (PTD <37 weeks, small for gestational age [<10th centile], stillbirth or spontaneous abortion);

(ii) maternal grade ≥3 adverse event up to 14 days postpartum; and

(iii) infant grade ≥3 adverse event up to 28 days.

Neonatal death (≤28 days) was also evaluated. Pregnancy outcomes were available for 640 women (99.5%). 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 with dolutegravir + emtricitabine/tenofovir alafenamide (1.0%; *P*=0.019) than with dolutegravir + emtricitabine/tenofovir DF (1.5%; *P*=0.053) or efavirenz/emtricitabine/tenofovir DF (4.8%).

Maternal and infant adverse event outcomes were similar by arm. Therefore it is the conclusion of the writing group that tenofovir alafenamide may be prescribed for women living with HIV after the first trimester.

The efficacy of zidovudine monotherapy for prevention of vertical transmission is well known; transmission rate for women treated with zidovudine monotherapy and assigned to PLCS was 0.8% in the Mode of Delivery study [14]. It is not a recommended option for pregnant women with HIV as it cannot be continued postpartum.

Our recommendations for ART initiation in pregnancy are the same as for when a woman conceives on ART (see Table 6.1).

6.3.3	It is recommended that an integrase inhibitor-based regimen be considered as the third agent of choice in patients: • With high baseline viral load (>100,000 HIV RNA copies/mL) • Where cART is failing to suppress the virus.	 2C 1C

Raltegravir and dolutegravir (from 6 weeks' gestation) may be used in this context. A retrospective cohort analysis of 92 pregnant women with HIV showed more rapid viral suppression in those patients on an integrase inhibitor-containing regimen versus women on ART without an integrase inhibitor [15]. Median time to viral load reduction by greater than 1 $\log_{10}$ unit was 7 days in the integrase inhibitor-containing ART arm and 35 days in the non-integrase inhibitor ART arm (P<0.01). In a second retrospective study of 14 women, raltegravir was either initiated as part of a cART regimen in nine antiretroviral-naïve women or added to an existing antiretroviral regimen in five women who had conceived on cART but had persistent viraemia [16]. Raltegravir was initiated at a gestational age of 34 weeks or later. The median exposure time to raltegravir was 17 days and the mean viral load decline was 2.6 $\log_{10}$ units. Raltegravir was well tolerated but elevated liver enzymes were reported.

6.4 Late-presenting woman not on treatment

6.4.1	A woman who presents after 28 weeks should commence cART without delay.	1B
6.4.2	If the viral load is unknown or >100,000 HIV RNA copies/mL, a three- or four-drug regimen that includes raltegravir 400 mg bd or dolutegravir 50 mg od is suggested	2D

Late presentation after 28 weeks and before the onset of labour occurs less frequently since the introduction of the routine offer and recommendation of antenatal HIV screening. With improved turnaround times for viral load testing, a woman presenting beyond 28 weeks may still be managed with a view to a possible vaginal delivery if she commences cART and achieves a viral load of <50 HIV RNA copies/mL by 36 weeks.

As discussed in section 6.7.3, an integrase inhibitor-based cART regimen is recommended because of a more rapid viral load decline compared to other drug combinations. A recent Thai study [17] of 57 pregnant women has shown that intensification of a standard three-drug cART regimen in women with detectable viral load after 28 weeks resulted in a significant reduction in viral load at delivery.

A pilot study in 40 women demonstrated that initiation of raltegravir-based therapy, compared to lopinavir/r-based therapy, resulted in significantly more women with undetectable viral load <50 HIV RNA copies/mL at delivery and a faster median time to viral load reduction to <50 HIV RNA copies/mL of 44 days in the raltegravir arm and 69 days in the lopinavir/r arm [18]. Adverse event incidence rates were also lower in the raltegravir arm. Raltegravir has been demonstrated to be more effective than efavirenz at reducing the viral load to <50 HIV RNA copies/mL by 36 weeks' gestation in an RCT of women who present after 28 weeks' gestation [19]. Similarly, the use of dolutegravir in the third trimester is more effective in reducing viral load to <50 HIV RNA copies/mL than other third agents [20]. Based on these emerging data, the writing group recommends initiation with raltegravir- or dolutegravir-containing regimens in this group of patients. Thus, where the viral load is unknown or >100,000 HIV RNA copies/mL, a fourth drug, raltegravir or dolutegravir, may be added to the cART regimen.

6.4.3	Management of an untreated woman presenting in labour at term.	

	All women should be given a stat dose of nevirapine 200 mg;	1B
	and commence oral zidovudine 300 mg and lamivudine 150 mg bd;	1B
	and raltegravir 400 mg bd;	2D
	and receive intravenous zidovudine for the duration of labour.	2D
	Please also see section 9.1.3 for HIGH-RISK neonatal management.	

A single dose of nevirapine, regardless of CD4 cell count (even if available) or hepatitis status, should be given immediately as this rapidly crosses the placenta and within 2 hours achieves, and then maintains, effective concentrations in the neonate for up to 10 days [21,22]. cART should be commenced immediately with oral zidovudine and lamivudine and with raltegravir as the preferred additional agent because it also rapidly crosses the placenta [23]. Intravenous zidovudine should be administered for the duration of labour and delivery. Following a loading dose of 2 mg/kg for 1 hour the maintenance dose of 1mg/kg per hour is infused until the cord is clamped [24]. Data from the French cohort indicate that peripartum zidovudine infusion further reduces transmission in women on cART from 7.5% to 2.9% (*P*=0.01) where the delivery viral load is >1000 HIV RNA copies/mL. However, this benefit is not seen if neonatal therapy is intensified [25]. If delivery is not imminent, a CS should be considered.

6.4.4	In preterm labour, if the infant is unlikely to be able to absorb oral medications consider the addition of double-dose tenofovir DF to the treatment described in recommendation 6.4.3 to further load the infant.	2C

Nevirapine and raltegravir should be included in the regimen as they cross the placenta rapidly (see above). In addition, double-dose tenofovir DF (490 mg) has been shown to cross the placenta rapidly to preload the infant, and should be considered where the prematurity is such that the infant is likely to have difficulty taking oral PEP in the first few days of life [26].

6.4.5	Women presenting in labour/with spontaneous rupture of the membranes (SROM)/requiring delivery without a documented HIV result must be advised to have an urgent HIV test. A reactive/positive result must be acted upon immediately, with initiation of interventions to prevent vertical transmission of HIV without waiting for further/formal serological confirmation.	1D

If the woman's HIV status is unknown due to lack of testing, a point-of-care test (POCT) should be performed. Women who have previously tested negative in pregnancy but who have an on-going risk of HIV should ideally also have a repeat fourth-generation laboratory test or, if unavailable, a POCT if presenting in labour. If the test is positive (reactive) a confirmatory test should be performed, but treatment to prevent vertical transmission should commence immediately. Where a POCT is not available, laboratory-based serology must be performed urgently including out of hours, and the result acted upon as above. Baseline samples for CD4 cell count, viral load and resistance should be collected. Treatment should be commenced immediately as per recommendation 6.4.3 above. Three-drug PEP should be given to the neonate (see section 9).

6.5 Evidence on teratogenicity, neonatal outcomes and ART

Pregnant women with HIV remain a special group with specific guidelines for HIV treatment based on teratogenicity and toxicity data on cART use in pregnancy from published reports, national HIV in pregnancy databases and international antiretroviral databases such as the APR.

The APR provides the best data on teratogenicity and first trimester ART exposure although it should be noted that births from the UK contribute to only 4.6% of collected data [27]. This voluntary prospective database records rates of congenital birth defects in babies born to women with first-trimester exposure to ART in comparison to background rates of congenital birth defects and second- or third-trimester only exposures to the same compounds. The congenital malformation rate observed in babies exposed to a specified drug is reported once a minimum of 200 prospective first-trimester exposures to an individual antiretroviral have been reported.

As of January 2018, the APR report for infants exposed to antiretrovirals includes the following.

- Abacavir, atazanavir, lamivudine, emtricitabine, lopinavir, nevirapine, ritonavir, tenofovir DF and zidovudine: there are now more than 200 prospective reports of first-trimester exposure with no signal of increased risk, and a greater than two-fold higher rate than in the general population has been excluded [27].
- Darunavir, efavirenz, indinavir, raltegravir and rilpivirine have been shown to have congenital malformation rates within the expected range, and a congenital malformation rate greater than 1.5-fold higher than in the general population has been excluded.
- For newer agents (cobicistat, dolutegravir, elvitegravir and tenofovir alafenamide) and a number of less commonly prescribed older compounds (saquinavir, fosamprenavir, enfuvirtide, tipranavir, maraviroc and etravirine) there have been insufficient reported outcomes of first-trimester exposure to exclude such risk.

Data from the APR have shown no difference in risk of birth defects for abacavir/lamivudine and non-abacavir/lamivudine backbones [28].

The PROMISE study [2] compared the efficacy of zidovudine/single-dose nevirapine with two combination therapy arms to prevent vertical transmission. The first combination consisted of zidovudine/lamivudine/lopinavir/r and the second comprised tenofovir DF/emtricitabine/lopinavir/r. An unexpected higher rate of early neonatal death, predominantly attributed to preterm birth, was reported in the tenofovir DF/emtricitabine/lopinavir/r combination therapy arm. On review of this large randomised controlled trial, the BMJ Clinical Guidelines group recommended the zidovudine/lamivudine-based antiretroviral regimen over tenofovir DF/emtricitabine with lopinavir/r, because of the reduced risk of infant death [29]. Other reviews have reported no increase in birth adverse events or safety events (and no increased risk of congenital abnormalities) in infants exposed to tenofovir DF compared to non-tenofovir DF-containing regimens, which did not have lopinavir/r as a backbone [30-33]. In addition to these systemic reviews, three prospective observational cohorts in pregnancy have shown no differences in adverse outcomes between tenofovir DF/emtricitabine and non-tenofovir DF/emtricitabine backbones [34-36]. Zash *et al.* [35] found that the risk of adverse birth outcome was lowest among infants exposed to a combined regimen of tenofovir DF/emtricitabine and safer than with zidovudine/lamivudine as a backbone. The writing group notes that the dose of lopinavir/r was increased by 50% for the duration of the third trimester in the PROMISE study. This is not standard practice and the writing group recommends against using lopinavir/r at this dose. On review of all the data the writing group does not consider the increase in adverse outcomes in the PROMISE study to be related to the tenofovir DF/emtricitabine backbone alone, but to the combination used (www.bhiva.org/BHIVA-response-to-BMJ-article). The writing group therefore recommends against using the combination tenofovir DF/emtricitabine/lopinavir/r in pregnancy. See also section 6.7.1 and Appendix 3.

An initial meta-analysis on the use of dolutegravir in six studies and from four control databases suggested it appeared safe to use in pregnancy [37]. However, a preliminary unscheduled analysis of an ongoing birth surveillance study in Botswana reported an increased risk of neural tube defects among infants of women who become pregnant while taking dolutegravir-based regimens [38]. The study reported four cases of neural tube defects out of 426 infants born to women who were on dolutegravir-based regimens at the time of conception. This rate of 0.94% compares to a rate of neural tube defects of 0.12% among infants born to women taking non-