6.7.4 PIs

While ritonavir-boosted PI therapy can maintain suppression of viral load, vertical transmission of HIV would be almost entirely dependent on antiviral activity within the woman. With minimal transplacental transfer, the low to undetectable drug concentrations in the fetus provide no peri-exposure protection. The writing group therefore recommends that, where possible, patients who conceive on PI monotherapy should have their regimen intensified with agents that cross the placenta.

Pharmacokinetic and safety data in pregnancy for cobicistat-boosted PIs show low darunavir exposure during the second and third trimesters of pregnancy which may be associated with virological failure based on a pharmacokinetic study of six pregnant women [95]. Compared with levels 6–12 weeks postpartum, where mean exposure of darunavir boosted with cobicistat was 90%, darunavir levels were lower in the second (56%) and third trimesters (50%). Cobicistat exposure was 63% and 49% in the second and third trimesters respectively. Therefore darunavir/cobicistat should not be initiated in pregnancy and women receiving this combination as part of cART and who become pregnant should be switched to an alternative such as darunavir/r. When given with elvitegravir, cobicistat has been shown to have lower levels during pregnancy and it does not cross the placenta [93]. For this reason, the writing group recommends that the boosting agent is switched from cobicistat to ritonavir for women who conceive on a cobicistat-boosted PI regimen. When initiating PIs during pregnancy, it is recommended that ritonavir is the boosting agent of choice.

PIs are highly protein bound and placental transfer in humans appears to be limited. During the third trimester of pregnancy, small reductions in protein binding can significantly increase free drug levels. For example, the protein binding of lopinavir reduces marginally to 99%, which results in 17% more unbound lopinavir [96]. It is therefore difficult to interpret the significance of studies that show reduced total plasma levels, with an increased likelihood of trough levels below the target during pregnancy. Compared with concentrations postpartum, concentrations of lopinavir/r 400/100 mg during the third trimester are reduced by 28%. The protein-free fraction is moderately increased (17%) and, at the standard dose, lopinavir appears to be clinically effective with a wide variation in individual plasma trough concentrations. A study using the tablet formulation showed that women taking three tablets bd (lopinavir/r 600/150 mg) achieved similar AUC levels to non-pregnant adults taking the standard dose of two tablets bd [97]. The improved bioavailability of the tablet formulation is also found in pregnant women and this, together with the impact of pregnancy on changes in protein binding, increases the protein-free fraction in the third trimester [98]. The writing group recommends that no dose adjustment is required in pregnancy for patients on lopinavir/r but notes that this treatment is no longer preferred for the reasons given above.

A study from Italy demonstrated similar atazanavir concentrations at standard 300 mg dose with ritonavir 100 mg od during the third trimester and postpartum [99]. However, recently third-trimester 24-hour AUC concentrations 28% lower than postpartum concentrations were reported from North America. Third-trimester concentrations of atazanavir in women taking tenofovir DF were lower still (i.e. approximately 50% of the postpartum values of women on atazanavir without tenofovir DF), and 55% of women in the study taking tenofovir DF had lower than target atazanavir concentrations. The study authors therefore recommended that it may be necessary to increase the dose of atazanavir to 400 mg (when given with ritonavir 100 mg od) during the third trimester [100]. A systematic review has demonstrated that grade 3–4 maternal hyperbilirubinaemia rates are doubled with atazanavir/r 400/100 mg [101]. Data from the Europe-based PANNA study also revealed a 33% reduction in third-trimester AUC and last measurable plasma atazanavir concentrations compared with postpartum. However, all drug concentrations measured, including with co-administered tenofovir DF, were above the recommended minimum plasma concentration for wild-type virus and therefore the writing group recommends consideration of an increased dose in experienced patients on an individual basis only if required [102].

Atazanavir/r 400/100 mg is also recommended in women who require an H2 antagonist during pregnancy, however the combination of atazanavir/r, tenofovir DF and an H2 antagonist is not recommended [101].

When prescribed with zidovudine/lamivudine, plasma concentrations achieved with atazanavir/r 300/100 mg od are only 21% less (by AUC) than historic controls whereas trough concentrations were reported to be comparable to these controls. Increasing the dose of atazanavir to 400 mg od during the third trimester increased trough concentrations by 39% and doubled the risk of hyperbilirubinaemia [103]. A case note review of 122 women in London receiving atazanavir/r did not show virological failure during pregnancy despite 83% receiving standard dosing of 300 mg with ritonavir 100 mg, and the authors concluded that the data did not support routine atazanavir dose escalation in pregnancy [67].

For darunavir, a study from the USA showed reduced troughs and 24-hour AUC values with daily dosing in pregnancy, whereas twice daily dosing produced levels more comparable to those in non-pregnant individuals [104]. The authors concluded that twice daily dosing should be used in pregnancy and higher doses may be required. For women receiving darunavir/r 800/100 mg, the AUC was reduced by 38% in the second trimester and by 39% in the third trimester compared to postpartum levels. With twice daily dosing the AUC was reduced by 26% in both trimesters. Similar findings have been reported from the PANNA network with subtherapeutic trough concentrations with 800/100 mg od dosing and no detectable darunavir in any of the cord blood samples collected [105]. Zorrilla *et al.* reported that, although total darunavir exposure decreases during pregnancy, there were no significant changes in unbound darunavir concentration compared with postpartum and concluded that no dose adjustment is required when darunavir/r is prescribed at 600/100 mg bd [106]. Others have also reported that although there is a reduction in darunavir levels during pregnancy, this is less pronounced when unbound darunavir levels are measured [105,107].

A pharmacokinetic study by the IMPAACT P1026s study group showed no impact on third-trimester darunavir levels by further increasing the dose from 600/100 mg bd to 800/100 mg bd, therefore this is not recommended [108]. The clinical relevance of these pharmacokinetic studies has yet to be fully determined.

It is the view of the writing group that if a patient conceives on darunavir-based cART and has a fully suppressed viral load on a daily regimen, this regimen may be continued. A more cautious approach using twice daily darunavir may be considered if initiating ART in pregnancy with darunavir or where there is known protease resistance. Although the pharmacokinetic data are consistent across studies, the virological impact during pregnancy and postpartum are unknown. Such outcome data are needed. Where the 600/100 mg bd dose is used, women should be reviewed postpartum for appropriateness to switch to the 800/100 mg od dose.

In general, there are still limited data on the currently available PI formulations. Given this lack of data and the considerable degree of interpatient variability, TDM for PIs during pregnancy can be considered, but is not routinely recommended in the absence of studies that show improved outcomes. If performed, TDM should be conducted at steady state (2 weeks or more into therapy) and repeated in the third trimester.

6.7.5 Other agents

The pharmacokinetic profiles of enfuvirtide in pregnancy, as well as of tipranavir and maraviroc, have not been described. It is noteworthy that enfuvirtide does not cross the placenta [109].

6.8 Stopping ART postpartum

6.8.1	Stopping ART after delivery is not recommended; women who wish to stop ART should be counselled on the risks and managed as per the BHIVA guidelines for the treatment of HIV-positive adults with antiretroviral therapy [5].	1B

6.9 HIV-2

6.9.1	Case discussion with experts with experience of managing HIV-2 is recommended for all women.	1D
6.9.2	A boosted PI-based regimen such as twice daily darunavir/r is recommended in women with HIV-2.	1C

Vertical transmission of HIV-2 is considerably less common than of HIV-1, varying between 0% and 4% in the absence of any intervention to reduce transmission [110-112]. It is likely that this can be explained by the lower viral loads seen in HIV-2 infection [112]. Nevertheless, vertical transmission can occur; of note, dual infection with HIV-1 and -2 as well as mono-infection can occur. There is no systematic evidence to guide choice of treatment for pregnant women with HIV-2 or PEP for the infant. Case discussion with experts with experience of managing HIV-2 is recommended for all women. A ritonavir-boosted PI-based regimen is recommended and tenofovir

DF/emtricitabine with twice daily darunavir/r would be likely to have the greatest anti-viral efficacy. It is suggested that such treatment is used, even in the presence of an undetectable HIV-2 viral load; this would help to avoid management difficulties if the viral load becomes detectable late in pregnancy. Agents used as PEP for the infant are a matter for expert opinion and discussion. Zidovudine monotherapy would be the minimum recommendation, but clinicians may wish to use triple therapy with raltegravir as a cautious approach and certainly if the viral load is detectable at delivery. Raltegravir is suggested because HIV-2 is sensitive to integrase inhibitors [113] and there is greater experience and availability of suitable formulations in paediatric dosing (see Appendix 3).

6.10 References

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