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5. Screening and monitoring of pregnant women living with HIV

5.1 Sexual health screening

5.1.1	Sexual health screening is recommended for pregnant women newly diagnosed with HIV.	1B
5.1.2	For women living with HIV and already engaged in HIV care who become pregnant, sexual health screening is suggested.	2C
5.1.3	Genital tract infections should be treated according to British Association for Sexual Health and HIV (BASHH) guidelines.	1B

There are limited data regarding the prevalence of genital infections in pregnant women living with HIV in the UK. Studies of pregnant women living with HIV in London and Slough found a prevalence of bacterial sexually transmitted infection (STIs) of 0–4% and of bacterial vaginosis (BV) of 1–4% [1-3]. A London cohort study found that STI diagnosis was associated with an antenatal HIV diagnosis, disclosing additional sexual partners during pregnancy, nulliparity, a shorter relationship duration and a partner of unknown HIV status [1].

The diagnosis and treatment of genital infections in any individual have clear benefits in terms of both individual-level morbidity and possible onward transmission to sexual partners. In pregnancy, the welfare of the baby is an additional issue. However, apart from the recommendation that all pregnant women should be screened for HIV, HBV and syphilis, asymptomatic HIV-negative pregnant women in the UK are not routinely screened for genital infections [4]. In pregnant women who are living with HIV, an additional consideration is the potential effects of the presence of a genital infection on vertical transmission of HIV. This could occur through an increase in the HIV viral load in the genital tract and/or the presence of chorioamnionitis. In addition, certain infections may be linked to premature birth, an event that occurs more frequently in women living with HIV when compared to HIV-negative women. An American study demonstrated that despite 96.9% of pregnant women living with HIV taking ART, a concomitant STI doubled the risk of spontaneous preterm birth [5].

It has long been recognised that genital infections, in particular ulcerative diseases, are associated with an increased risk of sexual transmission of HIV [6-8]. This may be a consequence of an increase in local HIV replication resulting in a higher viral load in genital secretions, secondary to the presence of specific microorganisms, and/or ulceration and inflammation [9,10]. Organisms associated with BV have been shown to stimulate HIV expression *in vitro* [11,12]. Studies from Kenya have demonstrated a reduction in cervical mucosal shedding of HIV RNA following treatment of gonococcal, chlamydial and non-specific cervicitis [13,14]. In the setting of full virological suppression on cART it is unclear to what extent, if any, the presence of any genital infection will contribute to the vertical transmission of HIV.

Viral load in cervicovaginal specimens has been shown to correlate with vertical transmission of HIV [15]. Genital tract HIV viral load will usually mirror the plasma HIV viral load [16], but there is increasing evidence of compartmentalisation of HIV between the plasma and genital tract. Genital tract HIV has been detected in women with an undetectable plasma viral load [17,18] and genetic diversity of virus from the two compartments has been reported [19]. A number of factors may be responsible for this, including differential drug penetration into body compartments and the presence of genital tract infections. With increasing numbers of women in the UK aiming for and achieving a vaginal delivery, an increasing number of babies are exposed to the cervicovaginal secretions of women living with HIV. The clinical significance of this is not clear. Data from the UK and Ireland [20] and France [21] show no difference in vertical transmission associated with mode of delivery in women with an undetectable viral load, providing some reassurance that the potential discordance may not be clinically relevant.

5.1.1 Herpes simplex virus

A systematic review has demonstrated a correlation between a herpes simplex virus type 2 (HSV-2) diagnosis and HIV vertical transmission (odds ratio [OR] 1.57). However, studies did not always adjust for key confounders such

as ART use and mode of delivery [22].

Regarding the relationship between genital HSV-2 shedding and vertical transmission, a Thai study found an association between vertical transmission and HSV-2 shedding in cervicovaginal lavage fluid at 38 weeks' gestation (OR 3.0), but this was no longer statistically significant after adjustment for ART use, maternal CD4 cell count, plasma viral load at delivery and cervicovaginal HIV viral load at 38 weeks (OR 2.3) [23]. Two other studies assessed shedding either at 10–32 weeks' gestation or at delivery, but neither found an association with intrapartum or *in utero* transmission in univariate analyses [21,24].

For pregnant women receiving ART, data regarding the relationship between vertical transmission and HSV-2 are inconclusive. A Ukrainian study, in which 96% of women received antenatal ART (half receiving cART), found no evidence that HSV-2 seropositivity was associated with risk of vertical transmission of HIV in unadjusted analyses. In multivariable analyses, the only factor associated with vertical transmission of HIV was lack of antenatal ART, which was associated with a three-fold increased risk. However, due to the relatively low HIV transmission risk (in comparison with earlier studies examining HSV and vertical transmission of HIV), the study was only powered to rule out a 2.25-fold increased risk of vertical transmission of HIV with HSV-2 antibodies [25]. A Thai study of women living with HIV who were HSV-2 seropositive found that vertical transmission of HIV was not reduced by zidovudine treatment [23].

That there may still be an increased risk associated with HSV shedding with patients on cART is suggested by a randomised, double-blind, placebo-controlled trial of herpes-suppressive therapy in women living with HIV and HSV-2 taking cART in Burkina Faso, which demonstrated that valaciclovir 500 mg bd further reduced genital HIV replication in those women with residual HIV shedding despite cART. However, vertical transmission of HIV was not reviewed [26]. A study from the USA reported greater rates of HSV-2 shedding at delivery in HSV-2-seropositive women with HIV compared to HIV-negative women (30.8% *vs* 9.5%). However, it is not clear whether any women were receiving antiviral HSV suppressive therapy, or what proportion of women living with HIV was receiving ART [27].

The incremental benefit of providing HSV suppression in late pregnancy to women living with HIV with a previous diagnosis of genital HSV and who are taking cART needs further investigation. These women should be treated in line with the BASHH/RCOG guidelines, which recommend that women who are HIV antibody positive and have a history of genital herpes should be offered suppressive aciclovir 400 mg three times daily from 32 weeks of gestation, especially where a vaginal delivery is planned. This aims to reduce the risk of transmission of HIV infection, and to reduce HSV shedding and herpes recurrence at delivery [28].

5.1.2 Chorioamnionitis and BV

Chorioamnionitis may lead to premature rupture of the membranes with the possibility of premature birth [29,30]. Chorioamnionitis, prolonged rupture of membranes and premature birth have all been associated with vertical transmission of HIV and may be interlinked [31-33]. However, a Phase 3 clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV transmission showed no benefit in reducing vertical transmission in the context of single-dose nevirapine prophylaxis [34]. Although both *Chlamydia trachomatis* and *Neisseria gonorrhoeae* have been associated with chorioamnionitis, the organisms usually implicated are those associated with BV including *Ureaplasma urealyticum* [35,36]. A strong association between BV and premature delivery has been reported [37,38]. There are data from Malawi that suggest that BV may be associated with an increased risk of maternal HIV acquisition in pregnancy as well as premature delivery and vertical transmission of HIV [36]. A study in which women received zidovudine from 34 weeks of pregnancy reported that maternal fever >38°C and BV were associated with *in utero* transmission of HIV with 2.6-fold and 3.0-fold increased risks, respectively [39]. It is not known how applicable this is in settings in which women receive cART from earlier in pregnancy.

In HIV-negative women, data regarding the effect of screening for and treating BV on premature delivery are conflicting. There are scant pre-cART data on women living with HIV, therefore BV should be treated as per BASHH guidelines (www.bashh.org/guidelines).

5.1.3 STI screening

In the setting of full virological suppression on cART it is unclear to what extent, if any, the presence of any genital infection will contribute to the vertical transmission of HIV. Pregnant women newly diagnosed with HIV should be

screened for STIs as per the routine management of newly diagnosed patients [40]. For pregnant women living with HIV and already engaged in HIV care, in the absence of randomised controlled trials but for the reasons outlined above, the writing group suggests screening for genital tract infections including evidence of BV. This should be done as early as possible in pregnancy and consideration should be given to repeating this at around 28 weeks. Syphilis serology should be performed on both occasions. In addition, any infection detected should be treated according to the BASHH guidelines taking into account recommended treatment regimens in pregnancy, followed by a test of cure. Partner notification should take place where indicated, to avoid re-infection.

5.1.4 Cervical cytology

- With regard to cervical cytology, pregnant women living with HIV should be managed as per the guidelines for the NHS Cervical Screening Programme 2016 [41] and BASHH/BHIVA/FSRH Guidelines on the Sexual and Reproductive Healthcare of People Living with HIV [42]. Routine cytology should be reviewed but deferred until 3 months postpartum.
- A woman referred with abnormal cytology should undergo colposcopy in late first or early second trimester unless there is a clinical contraindication. For low-grade changes triaged to colposcopy on the basis of a positive HPV test, the woman's assessment may be delayed until after delivery.
- If a previous colposcopy was abnormal and in the interim the woman becomes pregnant, the colposcopy should not be delayed.
- If a pregnant woman requires colposcopy or cytology after treatment (or follow-up of untreated cervical intraepithelial neoplasia [CIN] grade 1), her assessment may be delayed until after delivery. However, unless there is an obstetric contraindication, assessment should not be delayed if the first appointment for follow-up cytology or colposcopy is due following treatment for cervical glandular intraepithelial neoplasia.
- The 'test of cure' appointment should not be delayed after treatment for CIN2 or CIN3 with involved or uncertain margin status. In these circumstances if repeat cytology is due, and the woman has missed her appointment prior to pregnancy, cytology or colposcopy during pregnancy can be considered. This should also be reviewed at the postnatal appointment (see section 10).

5.1.5 Contraception

A plan for contraception to be used postnatally should be discussed antenatally with each woman. Antiretrovirals may need to be changed postnatally to align with a woman's choice of contraception. Further guidance on contraception in HIV can be found in the BASHH/BHIVA/FSRH Guidelines on the Sexual and Reproductive Healthcare of People Living with HIV [42].

5.2 Laboratory monitoring of pregnant women living with HIV

5.2.1	Pregnant women who are newly diagnosed with HIV do not require any additional baseline investigations compared with non-pregnant women living with HIV other than those routinely performed in the general antenatal clinic.	1D
5.2.2	HIV resistance testing should be completed and results available prior to initiation of treatment [43], except for late-presenting women (after 28 weeks). Women should be encouraged to continue combination (c)ART post-delivery but, where they choose to stop cART, a further resistance test is recommended to ensure that mutations are not missed with reversion during the off-treatment period.	1D

In the case of late-presenting women, cART, based on epidemiological assessment of resistance, should be initiated without delay and modified once the resistance test is available.

5.2.3	In women conceiving on cART there should be a minimum of one CD4 cell count at baseline and one at delivery.	2D
5.2.4	In women who commence cART in pregnancy, a CD4 cell count should be performed as per routine initiation of cART with the addition of a CD4 count at delivery even if starting at CD4 >350	1C

	cells/mm^3.	
5.2.5	In women who commence cART in pregnancy, an HIV viral load should be performed 2–4 weeks after commencing cART, at least once every trimester, at 36 weeks and at delivery.	1C

Performing a viral load test at 2 weeks allows for a more rapid assessment of adherence and may be of particular benefit in a late-presenting woman.

5.2.6	In women commencing cART in pregnancy, liver function tests (LFTs) should be performed as per routine initiation of cART and then with each routine blood test.	1C

Hepatotoxicity may occur as a result of the initiation of cART and/or the development of obstetric complications such as obstetric cholestasis, pre-eclampsia, HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome and acute fatty liver. Close liaison with the obstetric team is recommended.

5.2.1 Failure to suppress

5.2.7	In the event that a woman who has initiated cART during pregnancy has not suppressed plasma viral load to <50 HIV RNA copies/mL, the following interventions are recommended: • Review adherence (including a full exploration of potential impacting factors) and concomitant medication; • Perform resistance test if appropriate; • Consider therapeutic drug monitoring (TDM); • Optimise to best regimen; • Consider intensification.	1C

For a woman who conceives on cART that is not fully suppressive or loses virological control during the pregnancy, these interventions should be undertaken as soon as possible. If treatment failure occurs when the infant is likely to be delivered prematurely and may be unable to take medication enterally, intensification should consist of therapies that readily cross the placenta such as double-dose tenofovir DF, raltegravir and single-dose nevirapine. See also section 6 for further information on ART and pregnancy.

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