British HIV Association guidelines on the management of opportunistic infection in people living with HIV: Considerations in pregnancy 2024

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1 Introduction

1.1 Background and epidemiology

AIDS-related complications are a common cause of maternal death worldwide and are responsible for a high proportion of maternal deaths in low-income countries; they are a significant contributing cause of maternal death in high-income countries, although the absolute numbers are small [1,2]. Their medical management is complicated by the requirement to balance the needs of the mother and the fetus.

As opportunistic infections in pregnant women living with HIV in the UK are rare, they should be managed with close collaboration between HIV specialists, obstetricians, neonatologists, paediatricians and pharmacists. Any case of confirmed or suspected opportunistic infection in pregnancy should ideally be discussed within a fetal medicine and infection multidisciplinary team (MDT). If an MDT is not available locally, a national MDT is available and can be contacted (caroline.foster5@nhs.net; a.bamford@nhs.net; hermione.lyall@nhs.net; laura.byrne@stgeorges.nhs.uk; y.gilleece@nhs.net).

It is important to understand the physiological changes that occur in pregnancy as they can affect the interpretation of test results, clinical findings and the pharmacokinetics of drugs used in pregnant women [1,3,4]. Absolute CD4 cell counts characteristically decrease during pregnancy. Furthermore, there is a shift from cell-mediated immunity (Th1 response) towards humoral immunity (Th2 response) which leads to an increased susceptibility to, and severity of, certain infectious diseases in pregnant women, irrespective of HIV infection, including toxoplasmosis, varicella and listeriosis [5]. There is an increase in cardiac output, plasma volume, red cell mass and glomerular filtration rate in pregnancy. Absorption of aerosolised medication may be affected by an increase in tidal volume and pulmonary volume. Placental transfer of drugs, increased renal clearance, altered gastrointestinal absorption and metabolism by the fetus may affect drug levels.

Therapeutic drug monitoring should be considered due to altered drug pharmacokinetics in pregnancy, and the potential for complicated multiple interactions between antiretroviral agents and many of the drugs used to treat opportunistic infections [3,6]. For information about drug safety during pregnancy and breastfeeding, see Appendix 1.

While this guidance refers to women and breastfeeding throughout, the writing group fully acknowledges that it is also applicable to pregnant transgender men and gender diverse individuals and also that some may prefer the term chestfeeding to breastfeeding. We endorse the use of person-centered, gender-inclusive language in healthcare settings according to the individual's preferences.

Guidance on supporting people living with HIV with opportunistic infections, including in pregnancy, can be found on the British HIV Association (BHIVA) website (https://www.bhiva.org/file/6225e44b53c49/OI-guidelines-supporting-patients.pdf).

A full review of these guidelines is due by 2029, with interim updates only if recommendations need updating in line with new data.

1.2 Diagnostic considerations in pregnant women living with HIV

In general, pregnant women with symptoms suggestive of an AIDS-defining illness should be managed and investigated in the same way as non-pregnant individuals.

1.2.1 Radiology

When choosing an imaging modality for the diagnosis of opportunistic infections in pregnant women, consideration should be given to the need for a rapid diagnosis and the potential harm of the investigation. The potential fetal doses of ionising radiation from different imaging modalities and the risk of childhood cancer were recently outlined by Wiles *et al*. [7]. Discussion between HIV specialists, obstetricians, senior radiologists and the pregnant woman is recommended.

If opportunistic infection in the lung is suspected, a chest X-ray may be carried out with little or no risk to the fetus [7]. An ultrasound scan is a safe option for imaging of the abdomen. A direct computed tomography (CT) scan of the fetus in the pregnant abdomen should be avoided where possible. Magnetic resonance imaging of the fetus and abdomen is considered safe at all stages of pregnancy, although use of gadolinium in pregnancy has been reported to cause an increased risk of inflammatory conditions and should be avoided where possible [8].

CT scans of the brain, thorax or limbs of the mother may be carried out with minimal exposure to the fetus. Modern CT scanners have little radiation scatter to areas outside the scanner itself, so the main radiation scatter that would affect the fetus during a thoracic CT

scan would be internally within the body of the mother. The use of contrast with CT scanning is permitted.

Pulmonary embolus (PE) is a leading cause of maternal morbidity and death, and suspected PEs need to be investigated and treated promptly. Ventilation and perfusion scans, or in some situations limited 'perfusion 'scans, are regarded as acceptable for cases of suspected PE in pregnancy. CT pulmonary angiogram (CTPA) scans are also being used more often and are becoming regarded by many as the investigation of choice for the diagnosis of PEs in pregnancy. Although CTPA is associated with low fetal radiation exposure, it does expose the mother's breast tissue to a relatively high radiation dose [7,9].

1.2.2 Other diagnostic procedures

There are no specific contraindications for lymph node biopsy, liver biopsy and lumbar puncture in pregnancy. Endoscopic procedures, including bronchoscopy and upper and lower gastrointestinal endoscopy, may also be undertaken if necessary [10].

1.3 Diagnostic considerations for the fetus and neonate

Where an opportunistic infection has been diagnosed, the fetus should be closely monitored, for example by serial high-resolution ultrasound scans and fetal cardiac monitoring, so that signs of disease, growth retardation, fetal distress or drug toxicity can be detected early [1,11]. A paediatrician or neonatologist with expertise in HIV and congenital infection should be involved, prior to delivery, in discussions about the management of opportunistic infections in pregnant women. An MDT approach is advised to include risk–benefit discussions about opportunistic infection treatment choices in pregnancy, fetal monitoring and early review of the neonate for signs of congenital infection, drug toxicity and teratogenicity.

1.4 Vertical transmission of opportunistic infections to the neonate

Congenital infections in the neonate have been described for a variety of opportunistic pathogens affecting the mother. These include *Mycobacterium tuberculosis* [12,13], *Cryptococcus neoformans* [14-16], cytomegalovirus (CMV) [17], *Pneumocystis jirovecii* [18,19] and *Toxoplasma* [20-22]. In some instances, it may be difficult to distinguish between congenital and early postnatal infection.

Neonates born to women living with HIV should be assessed by a paediatrician with expertise in HIV and other congenital infections, and where necessary actively screened for congenital infections using appropriate national and local guidelines and assessed for signs of teratogenicity or drug toxicity.

2 Methods

The scope, purpose and guideline topics were agreed by the writing group. The search (population, intervention, comparator and outcome [PICO]) questions were set and an independent systematic literature review carried out. The Medline, Embase and Cochrane Library databases were searched and the literature reviewed to address each question. The PICO questions and search strategies are outlined in Appendix 2.

Further details of the methodology can be found on the BHIVA website (https://www.bhiva.org/file/5d514ec9b503d/OI-guidelines-methods-general.pdf), including the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess and grade the evidence. Good practice points (GPPs) are recommendations, based on the clinical judgment and experience of the writing group, with which few clinicians are expected to disagree and for which evidence is unlikely to emerge as they are generally considered to be good practice.

3 Summary of recommendations

From Section 5.2 Treatment of PCP

- **We recommend that trimethoprim-sulfamethoxazole is the treatment of choice for PCP in pregnancy (Grade 1B).**
- **We suggest that trimethoprim-sulfamethoxazole is the preferred prophylactic agent against PCP in pregnancy, after the first trimester (Grade 2C). Trimethoprim-sulfamethoxazole prophylaxis should only be used in the first trimester after a careful review of the risks and benefits (GPP).**
- **We recommend not using primaquine in pregnancy as it can cause both maternal and fetal haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency (Grade 1B).**

From Section 5.3 Neonatal considerations

- **We suggest that all cases of PCP in pregnancy should be discussed with the paediatric infectious diseases team and all infants should be reviewed for signs of congenital infection and/or drug toxicity at birth (GPP).**

From Section 6.2 Antifungal treatment for candidiasis and cryptococcal infection

Candidiasis

- **We recommend that vaginal candidiasis during pregnancy is treated with topical imidazoles, such as clotrimazole or miconazole for 7 days (Grade 1B).**
- **We suggest that the first episode of oropharyngeal candidiasis should be treated with topical nystatin suspension or amphotericin B (Grade 2B).**
- **We recommend that systemic therapy with fluconazole or other azoles is avoided in pregnancy, other than a single low dose (e.g. 150 mg) of fluconazole after the first trimester (Grade 1B).**
- **We recommend that oesophageal candidiasis not responsive to topical agents or a single dose of fluconazole is treated with liposomal amphotericin B (Grade 1B).**

Cryptococcal infection

- **We recommend first-line therapy with liposomal amphotericin B, which should be the only treatment in the first trimester (Grade 1B).**

- **Flucytosine should not be used in the first trimester (Grade 1C), and only used in combination with liposomal amphotericin B in the second and third trimesters when potential benefits outweigh the risks (Grade 2B).**
- **We recommend that fluconazole or other azole treatment, maintenance therapy and secondary prophylaxis are avoided during pregnancy, and amphotericin B is continued for maintenance therapy and secondary prophylaxis, where tolerated (Grade 1B).**
- **We suggest that fluconazole could be considered after the first trimester when amphotericin B therapy is not tolerated and potential benefits outweigh the risks (Grade 2C).**

From Section 6.3 Neonatal considerations

- **We suggest that all cases of cryptococcal infection in pregnancy should be discussed with the paediatric infectious diseases team and all infants should be reviewed for signs of congenital infection and/or drug toxicity at birth (GPP).**

From Section 7.2 Treatment of toxoplasmosis

- **We recommend that pyrimethamine with sulfadiazine is the preferred treatment for toxoplasmosis in pregnancy (Grade 1B).**
- **We recommend that clindamycin with pyrimethamine or atovaquone are used as alternative options (Grade 1B).**
- **We recommend that sulfadiazine is not used after week 32 of pregnancy; clindamycin is a suitable alternative (Grade 1B).**
- **We recommend that pyrimethamine should be supplemented with folinic acid 15 mg daily (Grade 1B).**

From Section 7.3 Neonatal considerations

- **We suggest that all cases of toxoplasmosis infection in pregnancy should be discussed with the paediatric infectious diseases team and all infants should be reviewed for signs of congenital infection and/or drug toxicity at birth (GPP).**

From Section 8.2 Treatment of CMV

- **We suggest ganciclovir and its oral pro-drug valganciclovir as first-line treatment for CMV disease in pregnancy (Grade 2D).**
- **In CMV retinitis, if appropriate and in consultation with a multidisciplinary team including ophthalmologists and infection specialists, consider the use of localised therapy to minimise maternal and fetal risk in the first trimester (GPP).**

From Section 8.3 Neonatal considerations

- **We recommend that all neonates born to mothers with evidence of active CMV disease should be investigated for congenital CMV infection with CMV PCR using an appropriate sample (i.e. urine or saliva) in the first 21 days after birth (Grade 1A).**
- **We suggest that all cases of CMV infection in pregnancy should be discussed with the paediatric infectious diseases team and all infants should be reviewed for signs of congenital infection and/or drug toxicity at birth (GPP).**

From Section 9.2 Treatment of *Mycobacterium avium* complex

- **We recommend rifampicin, azithromycin and ethambutol as the first-line treatment of choice for DMAC in pregnant women (Grade 1B).**
- **We suggest that the use of primary prophylaxis against DMAC is not required for women with CD4 counts less than 50 cells/mm^3, and immediate HIV therapy is recommended (Grade 2A).**

From Section 9.3 Neonatal considerations

- **We suggest that all cases of DMAC in pregnancy should be discussed with the paediatric infectious diseases team and all infants should be reviewed for signs of congenital infection and/or drug toxicity at birth (GPP).**

4 Auditable outcomes

- Proportion of pregnant women in the first trimester with a CD4 count <200 cells/mm^3 for whom discussion around the risks of trimethoprim-sulfamethoxazole treatment or prophylaxis is recorded.
- Proportion of pregnant women with an opportunistic infection for whom there is a discussion with a paediatrician or neonatologist at the time of diagnosis of the infection.

5 *Pneumocystis jirovecii* pneumonia (PCP)

5.1 Presentation and investigations

There is some evidence from case studies that PCP in pregnancy may be more aggressive, with increased morbidity and mortality, than in non-pregnant women [23].

Investigation and diagnosis of PCP in pregnant women is the same as for non-pregnant adults.

5.2 Treatment

Recommendations

- **We recommend that trimethoprim-sulfamethoxazole is the treatment of choice for PCP in pregnancy (Grade 1B).**
- **We suggest that trimethoprim-sulfamethoxazole is the preferred prophylactic agent against PCP in pregnancy, after the first trimester (Grade 2C). Trimethoprim-sulfamethoxazole prophylaxis should only be used in the first trimester after a careful review of the risks and benefits (GPP).**
- **We recommend not using primaquine in pregnancy as it can cause both maternal and fetal haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency (Grade 1B).**

No large, randomised trials investigating the treatment of PCP have included pregnant and breastfeeding women [24]. Trimethoprim-sulfamethoxazole inhibits bacterial and, to a

lesser extent, human folate metabolism. Folate is essential for fetal development and folate deficiency has been associated with an increased risk of neural tube defects and other congenital anomalies [25]. Trimethoprim-sulfamethoxazole has been associated with cardiovascular anomalies and defects of the urinary tract in some studies [26]. Other studies, including a meta-analysis, have not found an increased risk of congenital malformations associated with trimethoprim-sulfamethoxazole use in pregnancy, including in the first trimester [27,28]. A nested control study from the Quebec Pregnancy Cohort (predominantly in women without HIV) found an increase in the rates of spontaneous abortion in pregnant women who took trimethoprim-sulfamethoxazole in pregnancy (adjusted odds ratio [AOR] 2.94, 95% confidence interval [CI] 1.89–4.57) [29]. However, the benefit of trimethoprim-sulfamethoxazole to treat PCP in pregnancy outweighs any potential harm and it should be used, including in the first trimester.

Folic acid at 0.4–5 mg/day is recommended for all pregnant women [30]. Some authors have advocated using higher-dose folic acid replacement to prevent fetal anomalies associated with anti-folate drugs [31]. However, others have reported PCP treatment failure in this context [32]. Therefore, doses above 0.4 mg daily should only be considered in the first trimester of pregnancy and on a case-by-case basis.

Steroids should be administered as per standard guidelines for the treatment of PCP in non-pregnant women. Steroids are generally considered safe in pregnancy, although a systematic review of case–control studies suggested a small increased risk of oral clefts [33]. However, other large population-based studies have not found an association between maternal steroids and congenital anomalies [34,35].

Alternative options are limited to dapsone with trimethoprim or atovaquone. Clindamycin is generally considered safe in pregnancy, but primaquine can cause both maternal and fetal haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency and is therefore not recommended. Dapsone has been used in pregnancy to treat leprosy and malaria and appears to be safe [36,37]. The risk of haemolysis in neonates with G6PD deficiency seems to be very low [38]. Limited data suggest that atovaqone is safe in pregnancy [39].

Chemoprophylaxis for PCP should be prescribed to pregnant women living with HIV in line with standard guidelines for non-pregnant individuals. It is important to remember that there is a false reduction in absolute CD4 count during pregnancy, especially during the

third trimester, and in such circumstances a CD4 percentage less than 14% can be used as an indicator for the need to commence PCP prophylaxis.

Trimethoprim-sulfamethoxazole is the preferred prophylactic agent against PCP in pregnancy. There are theoretical concerns over the safety of this drug in the first trimester, especially prior to the closure of the neural tube, and an alternative agent could be considered during this time. Possible alternatives include once daily dapsone, atovaquone or nebulised pentamidine.

5.3 Neonatal considerations

Recommendation

- **We suggest that all cases of PCP in pregnancy should be discussed with the paediatric infectious diseases team and all infants should be reviewed for signs of congenital infection and/or drug toxicity at birth (GPP).**

It is unclear whether congenital *Pneumocystis* infection can occur, although occasional case reports suggest it may be possible [40,41]. However, it is recommended that infants born to women treated for PCP in pregnancy should be reviewed by a paediatrician or neonatologist, mainly to rule out any teratogenic effects and/or toxicity of maternal drug treatment. If there are signs of possible *Pneumocystis* infection, the infant should be urgently reviewed and the case discussed with the local paediatric infectious diseases team.

6 Other fungal infections

6.1 Presentation and investigations

Vaginal candidiasis occurs more frequently in pregnancy; however, although it is supposed that other fungal infections are more common in pregnancy, there is little direct evidence to support this. Investigation of suspected fungal infections should be identical in pregnancy, except for considering the risk associated with radiological procedures (see Introduction).

6.2 Antifungal treatment for candidiasis and cryptococcal infection

Candidiasis

Recommendations

- **We recommend that vaginal candidiasis during pregnancy is treated with topical imidazoles, such as clotrimazole or miconazole for 7 days (Grade 1B).**
- **We suggest that the first episode of oropharyngeal candidiasis should be treated with topical nystatin suspension or amphotericin B (Grade 2B).**
- **We recommend that systemic therapy with fluconazole or other azoles is avoided in pregnancy, other than a single low dose (e.g. 150 mg) of fluconazole after the first trimester (Grade 1B).**
- **We recommend that oesophageal candidiasis not responsive to topical agents or a single dose of fluconazole is treated with liposomal amphotericin B (Grade 1B).**

Cryptococcal infection

Recommendations

- **We recommend first-line therapy with liposomal amphotericin B, which should be the only treatment in the first trimester (Grade 1B).**
- **Flucytosine should not be used in the first trimester (Grade 1C), and only used in combination with liposomal amphotericin B in the second and third trimesters when potential benefits outweigh the risks (Grade 2B).**
- **We recommend that fluconazole or other azole treatment, maintenance therapy and secondary prophylaxis are avoided during pregnancy, and amphotericin B is continued for maintenance therapy and secondary prophylaxis, where tolerated (Grade 1B).**
- **We suggest that fluconazole could be considered after the first trimester when amphotericin B therapy is not tolerated and potential benefits outweigh the risks (Grade 2C).**

Two case series illustrate that cryptococcal infection in pregnancy is associated with high maternal mortality and frequent stillbirths and miscarriages despite antifungal therapy [42,43]. There have been no reports of teratogenesis or other adverse pregnancy outcomes

with liposomal amphotericin B [44]. Flucytosine has been associated with teratogenesis when used in rats at high doses [45]; however, there are case reports of its use to treat cryptococcal meningitis during the second and third trimesters of pregnancy with healthy fetal outcomes [46,47].

Although single-dose fluconazole has not been associated with any birth defects in pregnancy [48], specific birth defects associated with continuous daily doses of fluconazole of 400 mg/day or more in the first trimester, including cardiac septal defects, have been suggested by one case report and a large case–control study [49,50]. Two studies have also demonstrated a higher risk of spontaneous abortion with fluconazole exposure in the first and second trimesters [51]. Hence national agencies have been re-evaluating guidelines for its use in pregnancy. In one case series, 12 pregnant Ugandan women with cryptococcal meningitis were described, five of whom received fluconazole in the second and third trimesters after amphotericin B therapy [43]. Although few of these pregnancies resulted in live births, no congenital abnormalities were detected.

Voriconazole has been strongly associated with teratogenicity in rats and there have been no reports of its use in humans during pregnancy [52]. Itraconazole is also not recommended in pregnancy due to teratogenicity in animals, however the findings of one case series suggested it may be safe in humans [53]. The echinocandins are not considered safe, given evidence of teratogenicity in animal studies, although no human data are available [54].

6.3 Neonatal considerations

Recommendation

- **We suggest that all cases of cryptococcal infection in pregnancy should be discussed with the paediatric infectious diseases team and all infants should be reviewed for signs of congenital infection and/or drug toxicity at birth (GPP).**

Candida infection in pregnancy is not known to have direct implications for the neonate. Infants should be reviewed if a woman has been treated with antifungal drugs with a potential risk of teratogenicity, especially during the first trimester.

Congenital cryptococcal infection has been reported, but appears to be rare [14-16]. Infants born to mothers with cryptococcal disease in pregnancy should be assessed for neonatal cryptococcal disease by a paediatrician or neonatologist soon after birth. If cryptococcal disease is suspected, advice on management should be sought from a local paediatric infectious diseases team.

7 Toxoplasmosis

7.1 Presentation and investigations

The risk of reactivation of *Toxoplasma gondii* increases at lower CD4 counts. Pregnant women with a low CD4 count and a history of *T. gondii* infection should be monitored for signs of *T. gondii* reactivation. Pregnant women with negative *Toxoplasma* serology, suggesting no previous exposure to *T. gondii* infection, should be advised about the behavioural risk factors for primary *T. gondii* acquisition and associated risk reduction strategies [55,56]. There is no evidence that toxoplasmosis is more severe when it occurs in pregnancy [57].

Investigation and diagnosis of toxoplasmosis in pregnant women is the same as for non-pregnant adults.

7.2 Treatment

Recommendations

- **We recommend that pyrimethamine with sulfadiazine is the preferred treatment for toxoplasmosis in pregnancy (Grade 1B).**
- **We recommend that clindamycin with pyrimethamine or atovaquone are used as alternative options (Grade 1B).**
- **We recommend that sulfadiazine is not used after week 32 of pregnancy; clindamycin is a suitable alternative (Grade 1B).**
- **We recommend that pyrimethamine should be supplemented with folinic acid 15 mg daily (Grade 1B).**

Toxoplasmosis in pregnancy should be treated in the same way as in non-pregnant individuals. Pyrimethamine and sulfadiazine are the drugs of choice in pregnancy, especially after the first trimester [58].

Pyrimethamine is a folic acid antagonist (inhibitor of dihydrofolate reductase). Folinic acid 15 mg daily is recommended as co-administration, as high-dose folic acid (5 mg) compromises the efficacy of sulfadiazine-pyrimethamine in pregnancy [59].

Although some folic acid antagonists are human teratogens, this does not seem to include pyrimethamine [60-66]. A few single case reports of defects have been documented following exposure in pregnancy to pyrimethamine, but no systematic studies are available. One case report described a severe defect of the abdominal and thoracic wall and a missing left arm in an infant exposed to pyrimethamine, chloroquine and dapsone in the first trimester. However, an association between the drugs and the defect has been questioned [58].

The safety of sulfonamides during pregnancy has not been determined, although sulfonamides do not appear to pose a significant teratogenic risk when used as single agents [58]. One study in humans demonstrated an association with birth defects, but a causative association could not be established as other factors, such as its use in combination with trimethoprim, may have had a role [58].

The sulfonamides readily cross the placenta to the fetus during all stages of gestation [67-74]. Equilibrium with maternal blood is usually established after 2–3 hours, with fetal levels averaging 70–90% of maternal levels. Significant levels may persist in the neonate for several days after birth when given to the mother near term. Sulfonamides are most likely to cause harm to the neonate if administered near to term. Toxicities that may be observed in the neonate include jaundice, haemolytic anaemia and kernicterus. Severe jaundice in the neonate has been related to maternal sulfonamide ingestion at term by several authors [75-80]. Premature infants seem to be especially prone to the development of hyperbilirubinaemia [79]. Haemolytic anaemia has been reported in two neonates and in a fetus following *in utero* exposure to sulfonamides [75,76,80]; both neonates survived. Because of the potential toxicity to the neonate, these agents should be avoided near term. Due to these concerns, we recommend that sulfonamides should not be used after week 32 of pregnancy and that clindamycin should be used instead. Clindamycin crosses the placenta, achieving serum cord levels of approximately 50% of the maternal serum level [81,82], and is generally considered safe in pregnancy. Clindamycin is an alternative option when there is intolerance to sulfonamides.

Secondary prophylaxis should be the same as for non-pregnant individuals.

7.3 Neonatal considerations

Recommendation

- **We suggest that all cases of toxoplasmosis infection in pregnancy should be discussed with the paediatric infectious diseases team and all infants should be reviewed for signs of congenital infection and/or drug toxicity at birth (GPP).**

The effect of maternal HIV on the risk of congenital *T. gondii* infection is unclear. Similarly, the impact of maternal *T. gondii* infection during pregnancy on the risk of vertical HIV transmission is not known. In the non-immunocompromised host, congenital infection is usually associated with primary infection in pregnancy. There have been case reports of *T. gondii* transmission to neonates following reactivation during pregnancy in women living with HIV [83,84], and not always in the context of severe immunosuppression [85].

The neonate known to be at risk of congenital *T. gondii* infection should be reviewed by a paediatrician or neonatologist soon after birth. When clinical findings or laboratory/radiology investigations are consistent with possible congenital *T. gondii* infection, the case should be discussed with a local paediatric infectious diseases specialist to guide further investigation and medical management [86,87].

8 Cytomegalovirus

8.1 Presentation and investigations

The main focus of this guidance is the management of symptomatic CMV disease presenting as an opportunistic infection in pregnant women living with HIV. A detailed review of the management of all CMV infection and its impact on the pregnancy is outside the scope of this guidance.

There is no evidence to suggest that CMV disease presents differently in pregnant and non-pregnant women [88]. It is estimated that 5–10% of maternal CMV infections are symptomatic. Both primary and non-primary infections (through reactivation or reinfection

with a different strain) can lead to CMV disease in the mother and congenital CMV disease in the fetus [89-91].

For pregnant women living with HIV, indications for investigation and treatment of suspected maternal CMV disease follow the same principles as for non-pregnant women. Investigation and interventions for possible *in utero* CMV infection of the fetus also mirror the guidance for pregnancies in women without HIV, taking into account that CMV infection diagnosed in the context of advanced HIV has a higher risk of transmission to the fetus [92]. All pregnant women should be advised about reducing the risk of acquiring infections such as CMV that are associated with congenital infection [93].

8.2 Treatment

Recommendations

- **We suggest ganciclovir and its oral pro-drug valganciclovir as first-line treatment for CMV disease in pregnancy (Grade 2D).**
- **In CMV retinitis, if appropriate and in consultation with a multidisciplinary team including ophthalmologists and infection specialists, consider the use of localised therapy to minimise maternal and fetal risk in the first trimester (GPP).**

All licensed anti-CMV agents including ganciclovir, valganciclovir, foscarnet and cidofovir show adverse fetal effects in animal studies but there is a lack of adequate and well-controlled studies in humans. Any systemic therapy for the mother, especially in the first trimester, should be subject to a risk–benefit analysis with consideration of localised therapy if appropriate, for example intra-vitreal maintenance treatment of CMV retinitis to minimise the risk to both the mother and fetus [94].

The most clinical experience and case report data are available for ganciclovir and its oral pro-drug valganciclovir. We suggest ganciclovir and valganciclovir as first-line treatment for CMV disease in pregnancy. Minimal safety data exist for the use of ganciclovir and valganciclovir in pregnancy, and their use is recommended after considering the risks and benefits. Ganciclovir has been shown to be associated with teratogenicity in animal studies and is also mutagenic [95,96]. A 2023 pharmacovigilance study (not specific to women living with HIV) did not find any increased reporting of adverse pregnancy outcomes or birth

defects with ganciclovir/valganciclovir when compared with the use of aciclovir/valaciclovir during pregnancy [97]. There is evidence from case reports for the safe use of ganciclovir in the first and second trimesters for pregnant women in the post-transplant setting [98-100]. Of relevance to pregnant women living with HIV, there are case report data showing safe use of ganciclovir in the second and third trimesters to treat maternal CMV disease, with variable success in preventing vertical transmission of congenital CMV infection [101-105]. In one case of ganciclovir use, maternal and fetal death were reported, probably related to underlying CMV disease rather than treatment [106].

Foscarnet has been associated with fetal skeletal abnormalities in animal studies [107,108]. A single case report demonstrated the safe use of foscarnet in the second trimester of pregnancy for a non-CMV indication with no adverse fetal effects [109]. A further case of foscarnet use in the third trimester for a non-CMV indication reported neonatal death; it is unclear whether this was related to the treatment [110]. Due to the potential for renal toxicity, careful monitoring of amniotic fluid for oligohydramnios should be undertaken, especially in the second and third trimesters.

Cidofovir has been shown to be embryotoxic in animal studies, including rat and rabbit models. It is associated with fetal soft tissue and skeletal abnormalities. There are no data on the clinical use of cidofovir in pregnant women and its use is not advised [111].

Outside the context of CMV as an HIV-associated opportunistic infection, there is increasing evidence to suggest that valaciclovir at high doses can reduce the incidence of congenital CMV infection following maternal CMV infection, especially in the first trimester. This is an area of ongoing review and treatment of asymptomatic CMV infection during pregnancy (for those with or without HIV) with the sole aim of preventing congenital infection may be appropriate in some cases and should be discussed with the mother and relevant multi-disciplinary team on a case-by-case basis [112,113].

8.3 Neonatal considerations

Recommendations

- **We recommend that all neonates born to mothers with evidence of active CMV disease should be investigated for congenital CMV infection with CMV PCR using**

an appropriate sample (i.e. urine or saliva) in the first 21 days after birth (Grade 1A).

- **We suggest that all cases of CMV infection in pregnancy should be discussed with the paediatric infectious diseases team and all infants should be reviewed for signs of congenital infection and/or drug toxicity at birth (GPP).**

There is evidence to suggest that neonates born to women living with HIV not on antiretroviral therapy (ART) are at higher risk of developing congenital CMV infection than those born to mothers on ART, however data on the subsequent impact and rates of congenital CMV disease are scarce [92,114-116]. We recommend vigilance for signs of congenital CMV in neonates born to women living with HIV, especially those born to mothers who have CD4 counts <200 cells/mm^3 (<14%) or who are not on ART. These neonates should be assessed for signs and symptoms of congenital CMV infection. Audiology assessment according to national guidance should be ensured. There is no strong evidence to support CMV PCR screening of all infants exposed to HIV. The same pathways as for the general population should be followed.

In view of the higher risk of vertical CMV transmission, all neonates born to mothers with evidence of active CMV disease should be reviewed and investigated for congenital CMV infection with CMV PCR using an appropriate sample (i.e. urine or saliva) as soon as possible after birth and within the first 21 days of life and discussed with the paediatric infectious diseases team. The same pathways for investigation and management of possible congenital CMV should be followed as for the general population.

9 *Mycobacterium avium* complex

9.1 Presentation and investigations

There is no evidence to suggest that disseminated *Mycobacterium avium* complex (DMAC) disease in pregnant women presents differently to that in non-pregnant individuals. Diagnostic tests and treatment indications are the same for pregnant women as for other adults.

9.2 Treatment

Recommendations

- **We recommend rifampicin, azithromycin and ethambutol as the first-line treatment of choice for DMAC in pregnant women (Grade 1B).**
- **We suggest that the use of primary prophylaxis against DMAC is not required for women with CD4 counts less than 50 cells/mm^3, and immediate HIV therapy is recommended (Grade 2A).**

Clarithromycin has been associated with birth defects in animal studies. However, data from the Quebec Pregnancy Cohort did not identify an increased risk of congenital malformations in 686 pregnancies with exposure to clarithromycin in the first trimester [117]. Furthermore, 401 women in Denmark who were exposed to clarithromycin in the first trimester showed no increased risk of congenital malformations [118]. However, several studies have shown an increased risk of spontaneous abortion following first trimester exposure to clarithromycin [118,119]. Of note, Muanda *et al*. in a nested case–control study within the Quebec Pregnancy Cohort did not control for the severity of infection, and their findings may have been due to maternal infection rather than drug exposure [119].

Azithromycin has not been associated with birth defects in animal studies and human studies have not identified any increased risk of congenital malformations in infants exposed *in utero* [117,120]. Muanda *et al*. found an increased risk of spontaneous abortion following maternal exposure to azithromycin in pregnancy. However, as for clarithromycin, maternal infection may have been the cause of their findings. Therefore, azithromycin is preferred as first-line treatment for DMAC disease in pregnant women and clarithromycin is not recommended.

Ethambutol and rifampicin have been widely used to treat *Mycobacterium tuberculosis* in pregnancy, without any teratogenic effects being identified and are therefore considered safe to use in treating pregnant women with DMAC infection. There are no data on the safety of rifabutin in pregnancy and therefore rifampicin is preferred when treating pregnant women [121].

9.3 Neonatal considerations

Recommendation

- **We suggest that all cases of DMAC in pregnancy should be discussed with the paediatric infectious diseases team and all infants should be reviewed for signs of congenital infection and/or drug toxicity at birth (GPP).**

Congenital/neonatal MAC disease has not been reported. Infants born to women treated for DMAC in pregnancy should be reviewed by a paediatrician or neonatologist to exclude drug toxicity or teratogenicity. If there are any concerns regarding possible infection, review with the local paediatric infectious diseases team is recommended.

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